COLD INJURY

Transactions of the Third Conference
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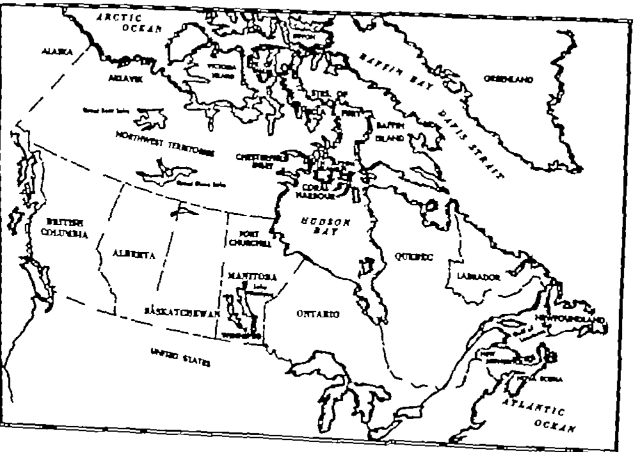

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Third Conference on Cold Injury

THE JOSIAH MACY JR FOUNDATION CONFERENCE PROGRAM

THE JOSIAH MACY JR. FOUNDATION has organized and devoted a large portion of its resources to the support of its Conference Program because the officers are cognizant of the fact that one of the major factors delaying scientific ad ance is the considerable obstruction to communication and mutual understanding across the many disciplines and specialties. It is felt that psychological as well as semantic factors contribute to the difficulty of communication people, even in arguments, are too much inclined to make statements *at* rather than to communicate *with* others. We tend to forget that the real question is whether or not our words and statements are those which are likely to convey to the listener the whole or even a small part of what we would like to express. I think we have learned that when communication is difficult it does not help to continue or to throw an angry note into one s voice We frequently fail to look for the other fellow s blind or deaf spots or the distorting lenses he carries, so that automatically everything said comes across to him wrong In the conferences conducted by the Foundation we strive to set the stage for meaningful communication.

The rapid growth of new knowledge and the increasing recognition that nature is of one piece makes it evident that the continued isolation of the many branches of science from one another is a serious obstacle to further progress Medical research and practice to be effective today must embrace data from all disciplines, the physical and biological sciences on the one hand and the psychological and social sciences on the other because advances in one field are frequently dependent upon knowledge deri ed from another discipline

We do not wish to compete with the scientific societies and journals which have established formats for the presentation of material their respective fields rather our aim at the conferences is to offer a very informal forum for the exploration of one another s views, feelings and attitudes and to encourage the exchange of methods, concepts, and difficulties in an atmosphere conducive to mutual understanding Although the fertility of the multidiscipline approach has been recognized by the scientific societies and journals which are usually restricted to one area or field in their coverage these organizations have not yet been able to establish adequate coverage of interdiscipline communication.

The Foundation through a series of two-and-a half day conferences has endeavored to meet this need for interdisciplinary communication by bringing together a small group of active investigators representing all the branches of science related to a chosen problem The participants, who meet annually in these informal meetings during the five-year period which each group is active, develop feelings of friendship trust and mutual admiration which promote communication, cross-fertilization and cooperation. Because the success of this experiment in communication is dependent upon participation by all members in the discussion, attendance at any conference is limited to twenty five.

Under the guidance of Dr Willard C. Rappleye, President of the Foundation since 1942, the Conference Program has been gradually expanded and enlarged until it now consists of nine different groups which meet annually to discuss a wide variety of problems in the field of medicine and closely related disciplines

In order to share the essence and tenor of these valuable conferences with as wide an audience as possible and give others an insight into the functions of the scientific mind, the informal nature and tempo of the discussions are preserved in the published transactions.

FRANK FREMONT-SMITH
Medical Director

INTRODUCTORY REMARKS

JOHN H TALBOT
Chairman

THE THIRD CONFERENCE ON COLD INJURY sponsored by the Josiah Macy Jr Foundation, was held at Fort Churchill Manitoba, Canada (see map frontispiece) because of a series of fortuitous circumstances In mentioning the inciting factor we have no choice but to implicate Colonel Blair and Dr Siple, of this conference, who had spent considerable time at Fort Churchill during the war years, and afterward. They knew it as a rugged outpost of tar paper shacks, where modern conveniences were unknown and where survival was difficult in any season of the year They also knew the new Fort Churchill, with its warm insulated buildings, laboratories for work, facilities for play and serviced by the best of utilities. It was their proposal at the Second Conference, that Fort Churchill should be the site of the Third Conference on Cold Injury

Negotiations with the Defence Research Board, Department of National Defence of Canada, were started a year ago through Dr O M Solandt As Director of this Board he was largely responsible, from the beginning, for their splendid cooperation.

Since we were primarily concerned with cold, it seemed advisable to hold our conference in the severest period of the winter which occurs during the last two weeks in February The week of the 21st was selected. Because the members of the conference, as well as guests, comprised Americans and Canadians it was necessary for several persons to obtain proper security clearance for admittance to the Canadian Military Post

On more than one occasion during the few weeks immediately prior to the meeting, Miss Rue, of the Josiah Macy Jr Foundation, intimated that we might be forced to hold the conference in New York rather than at Fort Churchill I rebelled against this idea Transportation by air to Winnipeg by commercial airlines is routine from Winnipeg to Fort Churchill it is best achieved in military equipment We owe a debt of gratitude to the Royal Canadian Air Force for this portion of our flight Squadron Leader G M Kightley Commanding Officer of the RCAF of Fort Churchill greeted us upon arrival and saw that our plane was *promptly dispatched at the conclusion of the conference.* Captain Chekaluk demonstrated outstanding skill as the pilot of our plane to

and from Winnipeg. The fact that we were able to adhere to a precise schedule permitted us to utilize our time at Fort Churchill to maximum advantage.

In order to be a passenger on an RCAF plane flying in the far North, it was necessary for each of us to have protective cold weather clothing available in flight We are grateful to Mr. A. C. Jones, of the Defence Research Board, who made sure that we were properly outfitted with superior items of cold weather gear These were excellent, and permitted us to spend a portion of our time out of doors during the conference days when sub-zero temperatures, and high winds, were routine. Upon arrival at Fort Churchill, the services of the Post were at our disposal through the courtesy of Colonel H. A. Millan, Commander and Lt. Colonel W E. Bowden, Assistant Commander

Last but not least was the Defence Research Northern Laboratories, where our sessions were held. Dr D B W Robinson, Director of the Laboratory provided excellent conference facilities, so that the scientific sessions were held under auspices as favorable as though we had assembled in New York Mr C. C. Simpson, one of his assistants, provided necessary transportation on the Post, and attended to the innumerable details which always arise in connection with the organization of a conference of this size.

Although I have singled out only a few persons, the list would have to be much longer if everyone were to be mentioned who had contributed to the success of this enterprise. Our Canadian friends were superb hosts, and each member and guest is deeply indebted to those who made the conference possible in one of the coldest communities in the world, and during one of the most severe weeks of winter

INTERRELATIONSHIP OF CIRCULATORY AND METABOLIC FACTORS

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OUR FIRST WORK in the cold was stimulated by a number of ideas which occurred to us while on actual field trips After some study on the human it seemed to me that these ideas should be tested by animal experimentation, so that dditional human experiments might be more reasonably planned These animal experiments were to deal with the variables which we had seen in our field trips. It was very fortunate that the work of E. A. Sellers, *et al* (1) J R Bla r ( ) and N H Mackworth (3) was being published at that time

First, I should like to provide background for the two points I shall discuss The first point concerns an apparent paradox the heat loss of n animal on the first day of exposure to cold is similar to its heat loss after 45 days of this exposure, but both the peripheral temperature and the central core temperature show marked differences at these two exposure times The second point concerns circulation in the extremities I shall present a summary of all these physiologic l factors f om the data that exist

Most of the data have been selected from rat and rabbit experiments, and the curves to be shown are from those experiments in which data secured in serial fashion illustrate the points elatively well I think, although there is oom for disagreement, that we ha e evidence that these data hold for other animals as well, and perhaps also for man

Figure 1 presents the sequence of events taking place in ats or rabbits during 40 to 45 days f exposure to cold I shall first summa ize the data in this figure

The first line graph n Figure 1 labeled *A* demonstrates the increase in heat production (1 4) Whether measured by direct or indirect lorimetry heat production of ats increases with exposu e to cold These ts usually kept t 24 C were exposed to 5 C There was an

The work here reported was supported in part by Contract AF [illegible] between the University of Washington and the Alaskan Air Command Arctic Aeromedical Laboratory Ladd Air Force Base Alaska

immediate increase in heat production noted, with a more gradual rise reaching a maximum somewhere between the 10th and 34th days The increase in standard metabolism (measured at control temperatures from 25 to 30 C.) is small, i e. 15 to 30 per cent (1 5 6)

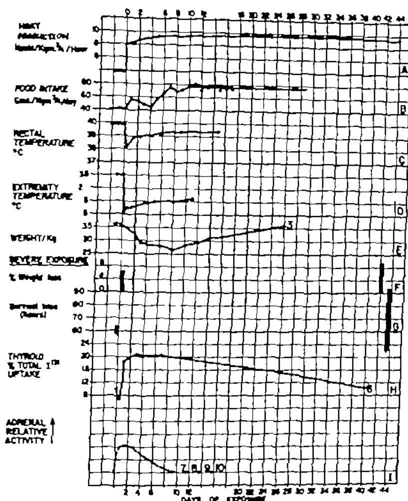


FIGURE 1 Summary f physiolgical changes during cold exposure. Each line represents a different function in relation t the days of exposure which are indicated along the abscissa. These are not necessarily simultaneous measurements. For discussion see text.

The second line graph, marked *B* summarizes food intake (4) Food consumption of rats increases little until the 4th or 5th day rising from the 5th day to a maximum at the 10th or 12th day at which time they

reach a steady state in which energy in equals energy out. Similar changes occur in rabbits.* In line *C* are shown the rectal temperature changes.* Rectal temperature drops rapidly when rabbits are moved from 30° to 5° C. and returns to a steady level, which is slightly lower than the temperature at the original 30° C., in from 6 to 8 days. If a rabbit which has previously been at 5° C. is placed at a still lower temperature, there will be only a slight drop in temperature and then the recovery pattern will occur. So during this stage in which the energy output rises sharply and quite early, i.e., ahead of the rise in food consumption, we have a shift in the central or so-called core temperature—actually the rectal temperature, as we measured it.

Acute exposure of nonacclimatized (+25° C.) rabbits to −45° C. causes a marked drop in rectal temperature (7). After 50 days acclimatization at −25° C., such exposure gives no drop in rectal temperature from the control level at −25° C.

Extremity temperature is depicted in line *D* of Figure 1. A good example of change in peripheral temperature is found in the rabbit ear. I have used it as an example here partly because I have good serial data on this animal. We find that when the rabbit is moved from 30° C. into a 5° C. room, its ear temperature drops markedly, then climbs over a period of days to settle at a little above 15° C. I think this is also true in the rat experiments we have done using the tail, ear and foot. Our data and those of Mackworth (3) and Malcolm Brown (8) indicate that this also happens in man, for example, in the human hand (9).

Herein then is depicted one of the most interesting points in the problem of cold exposure. An animal in its first hours of exposure to 5° C. is putting out as much heat (see line *A*, Figure 1), certainly within the range of 10 per cent, as an animal after 40 days at 5° C., and yet there is considerable difference in core and peripheral temperatures at these two times. The animal exposed one day has low rectal and peripheral temperatures.

Let us examine the weight change as shown in line *E* of Figure 1. Although given food *ad libitum*, these animals lose weight for approximately 8 days when moved from 30° to 5° C. In growing animals there will be a rather marked weight drop. The data in Figure 1 are taken from the weights of rabbits, although the response of rats is similar. If they are young growing animals, they will then start to gain weight, parallel to other animals, but if they are older animals, the weight will be stabilized at a lower level.

Weight loss with extreme exposure is illustrated in section *F* of Figure 1 (2). Nonacclimatized rabbits (kept at +25° C.) exposed to −50° F.

*Carlson, L. D. Unpublished data.

for 8 hours, lose less weight (6 per cent) than those acclimatized for 50 days at –25 C. (8.8 per cent)

In relation to survival time (7) after severe exposure (section *G* in Figure 1) rabbits moved from –25 to –35 C. survive 61 7 hours, while the average survival time for rabbits acclimatized at –25 C. is 93.2 hours

In reviewing the thyroid change (10) during cold exposure one notes that, when measured 2 hours after intraperitoneal injection, I^{131} in rat thyroid decreases in the first 6 hours in the cold, then increases to maximum in 4 days, and gradually declines to control level after 40 days in the cold. These changes are confirmed by the data on gland size (11) However data after 14 days in the cold indicate that the thyroxin requirement is inversely related to exposure temperature, that is, it is directly related to metabolic level (12)

The adrenal changes shown in Figure 1 (section *I*) represent a general guess. The adrenal cortex expands with cold exposure but contracts with increased ascorbic acid intake (13) We have learned that there is no increase in adrenal cortical requirement after 60 days in cold, as judged by the cortical extract requirement or by eosinophil response (14 15) The latter experiments have been confirmed (16) also, an immediate and early (6-hour) response in eosinophil level was demonstrated We also know that exposure to cold causes an immediate response of the adrenal, as evidenced by ascorbic acid and cholesterol indices and increased requirement for cortical hormone has been demonstrated with acute exposure (17)

Dugal What was the weight of the rats used in these experiments?

Carlson They weighed from 300 to 400 grams

Dugal And they lost weight at 5 C.?

Carlson In this particular experiment on weight change, section *E* of Figure 1 we used rabbits I have the figures if you like, for the rats as well. We have used male rats, both in the growing phase and in the more stable phase all along the growth curve. The data have been reported (4)

Horvath Was that 5 to 7 per cent weight loss shown in Figure 1 section *E*, the maximum at eight days?

Carlson Yes the fall was from 1 35 to 1.25 kg approximately 7 per cent Dr Blair (2) showed that after eight hours exposure to severe temperature, previously nonexposed animals lost less weight than animals exposed to cold for seven weeks. During this time, according to the data of Schachner *et al* (10) using radio iodine uptake as an index the thyroid passed through a transient change very rapid and marked in this range, and reverted back to normal.

During this period of cold exposure it is my guess, derived from a number of references in the literature, that this transient effect also occurs in the adrenal

Burch Was the iodine uptake an expression of greater activity of the thyroid and was this increased activity due to the fact there was so much vasoconstriction that blood was shifted to the thyroid, and therefore the thyroid was presented with more iodine? After all iodine is taken up by other tissues as well as by the thyroid

Carlson We are speaking of the iodine in the gland at the end of two to four hours. If the curve is extended to 24 hours the same result is obtained.

Burch. Once it is incorporated in the gland, it will remain there?

Carlson Yes If the curve is extended to 18 hours, the picture will still be the same I think the two-hour period is adequate to show the difference This has also been shown with the cell-height index (11) Dr Burch has a point in questioning this interpretation We are trying to check as these data do not indicate turnover

Burch. It may not necessarily indicate increased activity

Carlson I think it is a reasonable question, but this is our best data You may remember the data which were obtained with substitution therapy where the thiouracil-thyroidectomized animals required twice as much thyroid hormone to maintain the gland size in the cold (12) Unfortunately those experiments were not carried out at long-time intervals in the cold and what might be true here might not be true after 30 days

We hope that we are now acquiring data on this phase of the problem as one of my graduate students is studying the turnover using protein bound iodine (PBI) as well as thyroid iodine

I should like to turn now to our calorimetric data to show you what we have done We use thermal gradient calorimeters which are made in two sizes, one for rats and one for rabbits The temperatures can be varied by the surrounding bath of the calorimeter and the recordings are made in terms of the temperature difference across the thermal barrier

There are several experiments which might show the difference we have already indicated between the adapted and nonadapted animals Our procedure was first to take an animal from 30 C and put it in a 30 C calorimeter Next an animal from 5 C was put in a 30 C calorimeter Then a 30 C animal was exposed for two hours at 5 C. After which time there was a marked drop in rectal temperature and the animal was returned to a 30 C calorimeter

One of our original hypotheses derived from our field work was that there is a change in the core-shell relationships in these animals, which gives rise to this difference in the peripheral temperature. Curiously enough, we did not find the difference we had expected, but some of the explanations are in Figure 2. In an animal living at 30 C. and placed in a 30 C. calorimeter there was an initial rise in heat output which was essentially the ten minute time lag of the calorimeter. As the animal remained in the calorimeter the heat output gradually declined, for the animal was not particularly active.

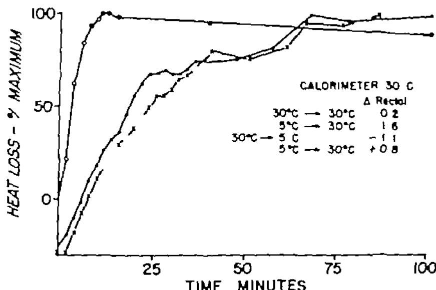


FIGURE 2. Direct calorimetry in rabbits. Initial rise in heat output indicates response time of calorimeter in rabbit indicated by symbol O, adapted to 30 C., which was then placed in calorimeter. Rabbit indicated by symbol was adapted to 5 C. and placed in calorimeter. Rabbit indicated by X, adapted to 30 C., was placed at 5 C. two hours before test in calorimeter. Changes in rectal temperature are shown in inset.

Blair. Was that the first time the animals were placed in the calorimeter or were they conditioned to it?

Carlson. They were conditioned to the calorimeter by many exposures. But this is not the kind of conditioning a psychologist would like, because we feel that we should leave a time interval, usually a week, between the experiments since these are fasting animals.

We did not see much difference in the heat output of 30 C. animals

as compared to 5° C. animals. The heat output was plotted in terms of 100 per cent response, so that the animals could be compared. The 30° C. animal, placed in the calorimeter at 30° C., had a very slight change (0.2°) in rectal temperature which may not be significant. An animal living at 5° C. for thirty days or more was brought out of the cold room and put directly into the calorimeter. You will note in Figure 2, that for a while the calorimeter supplied the animal with heat, causing it to warm along the curve shown by the solid dots. In almost all of our experiments, and this one is representative, the curve flattens slightly and then rises to the maximum level. During this time the animal's rectal temperature rose 1.6° C.

An animal taken from 30° C. and placed at 5° C. for two hours, showed a drop of one or more degrees in rectal temperature. The animal was then placed in the 30° C. calorimeter. Our data cannot show any significant difference between the two curves of heat loss, and yet in comparing the peripheral and rectal temperatures, we thought these looked markedly different.

The general warming of this animal seems to follow the same curve but the interesting thing is that this animal then regained most of the drop in rectal temperature. I feel that the reason we do not have a good distinguishing picture here, is that this 5° C. animal was essentially overheated when it was placed at 30° C. so that the ear temperature was about five degrees higher than that of the 30° C. animal.

The animal placed at 5° C. for two hours, when abruptly brought back to 30° C. behaves essentially as though there were increased heat input which was not being dissipated. The rise in rectal temperature has eliminated the possibility, I believe, of making the distinction between this core and shell arrangement.

Horvath: Did you say that this is increased heat output or input into the animal. It must be all heat input from the calorimeter.

Carlson: One would have to subtract the open dot curve in Figure 2, but this is heat input into the animal, which was the point we were interested in, namely seeing if there were any difference in the core and shell relationship. What we had hoped for was that the rectal temperatures would not show this marked change.

Horvath: Did you get the major rectal temperature change over the period of two hours, or in 25 minutes.

Carlson: That I cannot answer because we were attempting to use both direct and indirect calorimetry and in these calorimeters we were never able to have the rectal thermometer in during the entire time. From experiments which were made in the hot room itself, the rise in rectal temperature seems to be a gradual one.

Blair Did you try to chart that on semilog paper?

Carlson I have done this by taking the maximum heat output, and using the log of the difference from maximum and correcting for the lag The curve is linear on a semilog graph.

Blair And if you do not subtract at all?

Carlson. I have not tried that. The curve for the 30 C. animal incidentally is the same sort of curve one would obtain with any introduced heat source. It represents true calorimeter lag

Horvath I think what Colonel Blair means is that it looks like a simple exponential curve

Carlson Not with the flat portion.

Horvath It still rises. If one plotted it on semilog paper the data might fit into an exponential function. Is that your point?

Blair There would be some variations but I mean in a general way

Horvath The flat portion of the curve is there only for a short period of time is it not?

Carlson Yes. If I averaged all my data, the curve would not be accentuated as it is here, and would again be linear I obtain a much better linear curve using the initial plateau as my R_o rather than the final plateau. The linear curve plots the difference, which is the heat being supplied.

Pagé Do animals adapted to cold have a larger heat output at 30 C than nonadapted ones?

Carlson. In rabbits exposed to cold for 30 to 45 days, there was only a slight difference, which is not statistically significant.

Pagé At 30 C?

Carlson At 30 C. this would be a standard metabolism.

Horvath. When you take these animals out of the cold, do they show no increase in metabolism during the first few hours?

Carlson No there is no increase and that is perplexing.

Horvath Dr Hartman and I (18) were able to do essentially the same thing in 1938 As far as I remember the data showed that there was a supernormal metabolism in the first couple of hours after the animals had been exposed Have you tried these experiments with rats, as well as rabbits?

Carlson There are some real problems here One of them is that when one has a temperature change in a calorimeter the indirect method is invalid

Pagé Are they fasted at room temperature or in the cold?

Carlson They are fasted at the temperature at which they are living

Sellers For how long an interval?

Carlson. For fifteen hours

Sellers I should think a fast of fifteen hours in a rat of average weight would represent quite a stress in the cold, whereas it does not at normal room temperature Whether that would be true in the case of the rabbit I do not know but I wonder if that could affect the results you have observed

Carlson I have also run some of these animals immediately after feeding. Although there is more variation, essentially the same effect is obtained. The heat output is greater

Horvath Were these animals fed once during the day?

Carlson Yes and always at the same time The food was usually consumed within two hours.

Stevenson They were not fed *ad libitum?*

Carlson. Not rabbits because they continue to increase in weight We feed them to maintain weight

Cofey How was the activity of the rabbits controlled

Carlson They were relatively confined The calorimeter has a time response so that any burst of activity will appear on the record, but slight movements probably will not The slight changes due to movement cannot be distinguished from trapped air changes There were no bursts of activity on the record the animal usually sat very quietly

Burton Would it not be possible to think of the graph in terms of measuring the heat debt, the difference between the heat content of the animal in equilibrium at 5 C., and at 30 C That would be the inverted triangular area on Figure 2, would it not, between the final heat output line and the heat reaching the calorimeter? At each point the difference between the heat that is being produced and the heat that goes into the calorimeter is the heat going into the animal to warm him up There is no real difference between the acclimatized and nonacclimatized animal in the areas giving this heat debt Is that right?

Carlson Yes and this is disappointing from two standpoints (*a*) the areas are the same, and (*b*) the rise in rectal temperature was observed in the adapted animal I am hoping to conduct the experiment so that the rectal temperature will stay fixed, and thereby establish a relationship between core and shell.

Horvath Does this suggest that the term adaptation has no meaning, and that there is no such thing as adaptation or acclimatization in these animals?

Carlson This would require considerable discussion, and it is the reason for my preparatory remarks On the basis of my original presentation in Figure 1 there are differences which can be discerned I think adaptation is indicated if we remember that the 6-degree difference

(T_R—T) is from a depressed rectal temperature in one animal another animal actually had a rectal temperature above 40 C.

I think Dr Horvath made a good point in his earlier statements, and one that has perplexed me from the standpoint of factors regulating metabolism. The 30 C. animal had a caloric output of about 4 kilocalories while the 5 C. animal had an output of 8 kilocalories When they were put in the calorimeter at 30 C., the heat outputs were identical, at least within 10 to 20 per cent

Burch Is the ordinate percentage of maximal?

Carlson Yes.

Coffey What was the atmosphere in the calorimeter pure oxygen or balanced?

Carlson It was a continuous circuit type of indirect calorimeter An oxygen spirometer was used to supply the oxygen removed.

Coffey It was actually pure oxygen, B P oxygen, rather than normal?

Carlson I do not think one could say that, because the continuous circuit, in terms of gas flow is a closed system with a CO absorber and pump, and a T out to the spirometer so that any change in volume is compensated by additional gas from the spirometer

Brown May this not be a matter of the time involved? The contribution the shell makes would vary with the temperature, would it not, and after a certain time it is finished for a given temperature. Might you not have obtained different curves if there had been a different time interval for the second group?

Carlson The reason I used this time interval was that it gave the maximum change in rectal temperature.

Brown I can see that But earlier perhaps, don t you think you might have obtained a difference?

Carlson Possibly We ought to make a calorimeter in which we can change the temperature and still make calorimetric measurements so that we can keep the animal in the calorimeter It is very difficult to do, in my experience

I have done the reverse of this experiment that is, I have taken animals which had been at 30 C. and at 5 C., and exposed them to 5 C. in the calorimeter In doing this I found, as reported in Figure 2, that the level of heat output was very high. In spite of the similarity in the heat output between the 30 C. and the 5 C. animals, I could not dissociate any stimulus to the metabolism through a difference between the indirect and the direct methods But when I lowered the calorimeter temperature to —10 or —11 C., and exposed an animal from 30 C. and one from 5 C. a marked difference between direct and indirect calorimetric measurements appeared in each of these two animals.

The point brought out by Dr Horvath s questions, that we have an inexplicable rapid, marked change in metabolism, is not true in Figures 3A and 3B which show two examples of the experiments in which we exposed the animal to −11 C.

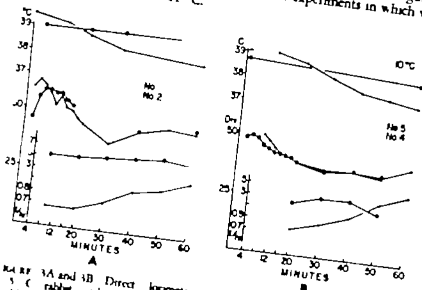


FIGURE 3A and 3B Direct calorimetry of rabbit at −10 C Rabbit O adapted to 5 C rabbit adapted to 30 C (Calibration 0 19 kg 1 div) Ordinate lower divisions on calorimeter Ordinate insert oxygen uptake in liters per hour STPD upper rectal temperature in degrees centigrade Abscissa time in minutes

In Figure 3A, the No 1 animal (rabbit) had been at 30 C and was brought directly into −10 C calorimeter There was a marked decrease in heat output as one would expect but later in the experiment there was an increase This I must confess, reverts us to the question of activity in the calorimeter It is quite obvious that during this period the animal was active because the calorimeter is by no means stable The animal that had been at 5 C (Rabbit O) before being placed at −11 C shows somewhat the same pattern in heat output

The oxygen consumption of these animals indicates that when the temperature is lowered very markedly there is an adjustment in metabolism which takes time The rectal temperature of the 5 C animal was maintained, whereas that of the 30 C animal decreased Our original statement that the heat output of these two animals was essentially the same, still holds

Figure 3B is a similar experiment Again, we used both a warm-

adapted (30 C.) and a cold adapted (5 C.) animal The rectal temperature of the 5 C animal dropped slightly but that of the 30 C animal showed a marked drop There was practically no distinction between heat outputs Occasionally the oxygen consumption curves intersected. This, I think, brings into some question our original supposition based on our studies in humans From the findings in Figure 3B one could say that after one hour metabolism contributed more to the heat output of the warm-adapted animal (solid dots) than to that of the cold-adapted animal. The supposition from the other figures is that the oxygen consumption curves might eventually intersect. But the activity in the calorimeter is extraordinary at this point. You may have noticed in Figure 3B that I occasionally lost the rectal thermometer during the tests and had to terminate them. The difference between indirect and direct calorimetry again shows up

Although in the 30 C animals there is at least some indication that I am stimulating metabolism, I still have the problem of the stimulus to metabolism in the 5 C animal which, within the limits of my system, is brought up very quickly to a new level At – 11 C the ratio of heat output for the 5 C animal will be approximately 5 3 and that for the 30 C. animal, approximately 5.2

This is a rather pronounced increase in heat output. The other dif ference observed here is that when an animal is moved from 30 C. to 5 C., it benefits by vasoconstriction. When the temperature is below *freezing, heat must be produced to prevent frostbite. There was no* frostbite in these experiments

Horvath Just where did the 5 and 30 -adapted animals start in their oxygen consumption?

Carlson The 5 C animals were started at 3 4 kilogram calories per kilogram ¾ per hour

Horvath They have almost a 100 per cent increase.

Carlson. Yes The direct and indirect calorimetric values are close to being in direct balance

Horvath What about the 30 C *animals?*

Carlson They start at about two-thirds of that (2.4) They are off the scale

Horvath The initial stimulus *seems to be of about the same magni*tude in both of them.

Carlson There is an initial stimulus in twenty minutes.

Horvath Of the same magnitude. The thing I am wondering about is this Dr Carlson you are apparently making a distinction between those two series of animals based on the fact that you were not able to stimulate one. It appears to me, at least indirectly that you have evi

dence of stimulation of both groups I may have missed your point I am not sure

Carlson You may have misunderstood me. The point is that at this low temperature the course of events may be lengthened so that the change in oxygen consumption can be seen Whereas one animal attained equilibrium of heat input-output within twenty minutes, the other animal reached equilibrium after an hour

Horvath There is a remarkable difference between those two groups of animals?

Carlson That would be my supposition

Burton May I put this in terms of my own thinking? You are telling us that with these two groups of animals in the low temperature calorimeter the heat received by the calorimeter in that time is not significantly different in the two cases In animals that have been adapted to 30 C most of that heat is coming initially from the cooling of the body and the rest from the metabolism In the case of the animals adapted to 5 C the heat th oughout that period is coming from metabolism and very little from the cooling of the body Is that right?

Carls n I think that would be stating it generally as long as one interprets your statement very little from the cooling of the body liberally enough, as Dr Horv th points out Although I do not have the data here there is an indication that the rectal temperature changes very little

Burton So, when placed in the cold calorimeter there is much more heat required by the animal that has been adapted to 30 C than the animal that has been adapted at 5 C

Carl n That is right, and is I think, reasonable from what we know The studies should be arried little further because the inc ease in oxygen onsumption of the 30 C animal is in excess after an hou at which time the imbalance reverses itself

Blair In omparing animals that are adapted to 5 C with those living at 30 C do you place the nimals d rectly from the 5 C env ronment int the cal rimeter or is there a period in which the animal is at oom temperature (30 C) before going nt the calorimeter

Carl n There is a very short period f less than tw minutes when the animal is weighed

Blair That w uld be of little significance but f it were a matter of hours it would make quite a difference

Editor s Note Dr Carlson would l ke t add the f ll wing om ments t his remarks at the conferenc

Animal exposed to different t mpe atures hange hei t pro duction in relatively short time A t at C ll ha double he

metabolism of one at 25 C., yet when the 5 C. rat is put at 25 C., its metabolism does not start at twice that of 25 C. rat and gradually reduce. It is within 30 per cent the metabolism of a 25 C. rat in the time interval (ten minutes) in which metabolism can be measured. Further rats rapidly increase their metabolism when placed at lower temperatures, the ability to increase and maintain metabolism being conditioned by the previous exposure temperature. This seems to indicate a heat production which is under immediate control, and would most likely originate from muscle.

Carlson Last year in Montreal, Drs. Scott, Thomas, and Sellers (18) reported some very interesting work concerning action potentials in muscle, and we have done some related work with these rabbits. There are two lines of evidence here, and I shall discuss my experimental technique so that you will know its limitations.

The first pertains to the use of radioiodine to determine the circulation within the rabbit ear and within a muscle of the hind limb, usually the hamstrings. The technique, as you know is one of introducing radioiodine and then measuring the time of disappearance. The time involved is a period of ten, or preferably twenty minutes. During this time our usual criterion was that the animal should not show obvious struggling. Data taken when there was obvious struggling were discarded.

The use of I^{131} I think must be accepted as a method which may show circulation but which is also related to the capillary permeability because the iodine must get into circulation in order to be removed.

Burch What is the preparation of iodine, the quantity and how was it injected?

Carlson Straight sodium iodide is obtained from Abbott Laboratories, usually 25 microcuries per ml. Very tiny quantities must be injected, less than 0.1 ml. It is not critical, as long as there is a count.

I shall give you first the experiments on the ear which I think should be regarded with caution (Table I). We always attempted to introduce the I^{131} just into the skin and in the midportion of the ear. Some measurements were made at 30 C., others at 5 C., and others at −20 C. This is the average of several experiments. Unfortunately I do not have sufficient data to feel assured about the 5 C. animals at 30 C. But this is a situation which is worth looking at and discussing because there is certainly a marked vasoconstriction when the 30 C. animal is placed at 5 C.

Although temperature measurements give evidence of increased temperature in the ear the circulation experiments above do not bear this out. The only explanation I have is that this is an area where there are many arteriovenous shunts and I do not know what A V shunts do

TABLE I

Rabbit Ear			
Original Environment	Experimental Environments 30° C.	5° C.	−20° C.
30° C.	0.44*	0.088	0.077
5° C.	——	0.044	0.023
Rabbit Leg Muscle			
Original Environment	Experimental Environments 30° C.	5° C.	−20° C.
30° C.	.093*	.096	——
5° C.	——	.137	.46

$$k = \frac{\log C_1 - \log C_2}{.4343\,(t_2 - t_1)}$$

C_1 = counts per minute at time t_1
C_2 = counts per minute at time t_2 (19)

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The difference shown above is very marked, and if borne out by further experiments, will be a rather interesting one. I present this as tentative data only because I do not have sufficient data to give a statistical analysis. These are preparatory experiments.

To allow Dr. Sellers to enter the discussion, I should like to indicate that at the time we were doing these experiments we used a pair of needle electrodes about two centimeters apart, which had about a centimeter exposed on each. They were thrust into the hamstrings, and over a period of an hour or more periodic samplings were taken of the electrical activity in the muscle. The differences we obtained are shown in Figure 4, which represents the electromyographic (EMG) data we have from the muscle action potentials. These data were collected from animals in their accustomed cages with the electrodes in place. Three different experiments are shown to indicate the results.

One animal from 30° C. was placed at −10° C. for six hours. You

metabolism of one at 25 C yet when the 5 C. rat is put at 25 C its metabolism does not start at twice that of 25 C. rat and gradually reduce. It is within 30 per cent the metabolism of a 25 C. rat in the time interval (ten minutes) in which metabolism can be measured. Further rats rapidly increase their metabolism when placed at lower temperatures, the ability to increase and maintain metabolism being conditioned by the previous exposure temperature This seems to indicate a heat production which is under immediate control, and would most likely originate from muscle.

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TABLE I

Rabbit Ear			
Original Environment	Experimental Environments 30 C	5 C	−20 C
30 C	0 44*	0 088	0 077
5 C	——	0 044	0 023
Rabbit Leg Muscle			
Original Environment	Experimental Environments 30 C	5 C	−20 C
30 C	093*	096	——
5 C	——	137	46

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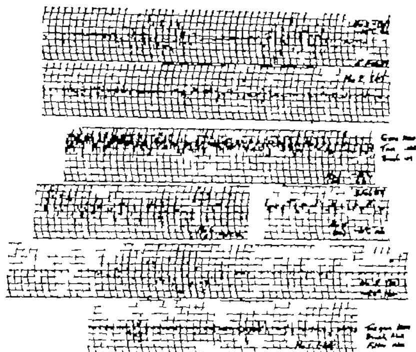


FIGURE 4. *Electromyograms from central portion of hamstring muscle in rabbits* using two-needle electrodes 2 cm. apart, 2.5 cm. long, with distal 1 cm. for recording From top to bottom 30 C. animal (No. 3) 5 C. animal (No. 2) 30 C. animal (No. 1) 5 C. animal (No. 6) after exposure to —10 C. six hours 30 C animal (No. 5) upon immediate exposure to —10 C. same animal exposed to —20 C one hour 30 animal (No. 1) after exposure to —20 C. 30 days.

will notice on the EMG alternate quiescence and marked activity However the animal from 5 C., which was placed at —10 showed a little more activity in the base line and yet less marked activity from shivering

On the bottom curve is the same relationship in the 30 C. animal placed at —20 C for a period of weeks You will notice here again the quiescent period followed by marked electrical activity another quiescent period, and again marked activity during which activity is continuous, with occasional bursts.

Occasionally the record assumes the relationships indicated in the center of the figure. There is a long period in which this activity will appear to be less than that of an animal from lower temperatures. It seems to be a prolongation of the difference we see in the base line. An animal at 30 C., to make a comparison with these two has considerably less activity in the EMG

I hope Dr Sellers will now speak about this the records would be quite different if presented in a summated EMG because of the sharp activity bursts of the nonadapted animal. The significance of muscle activity lies in the contrast between the background activity of the 5 C animal, and the silent period interrupted by marked activity in the muscle of the 30 C animal acutely exposed.

Our data on circulation changes should provoke a little more discussion from this group, which last time considered in detail the contributions of the liver to this increased heat response I think there is at least a possibility of indicating contributions of muscle to the heat response.

Sellers Dr Carlson I should like to ask you whether you did summated EMG s, which would gi e figures comparable to the results that we reported in Montreal (19)

Carlson No I am sorry I do not have that data

Sellers From looking at the raw data, I would not say that our results necessarily differed. Usually the muscle activity that we observed in animals which were adapted to 30 C and then exposed to cold was very vigorous Interspersed in the record were periods of relative inactivity I think probably our observations on the animal adapted to a freezing temperature would not be dissimilar to yours. The summed activity which we reported did show a significant difference in that the total activity of the nonacclimatized animals exposed to cold was considerably greater than that of acclimatized rats exposed to the same degree of cold

Recently we have been doing the same type of work in humans. There we find a difference in the appearance of the oscillographic tracing in that the human muscle is apparently completely inactive when the muscle is at rest There is no jiggling up and down of the base line it is flat. On the other hand when the muscle moves, or when shivering takes place, there is sometimes the rather solent activity we see in Dr Carlson s tracings.

I should like the views of the biophysicists and others who ha e had more experience than I have with the electromyograph, as to possible differences in technique which w ll result in the different findings in rats and in man that I have just reported. In the rats we always observed a basal activity The type of electrodes are of obvious importance In rats we used the whole length of a needle or a safety pin as the electrode, so presumably we were measuring the total activity of a certain amount of muscle mass rather than the activity of a few fibers I humans we have been using surface electrodes We have used needles, too tracing is just about the same

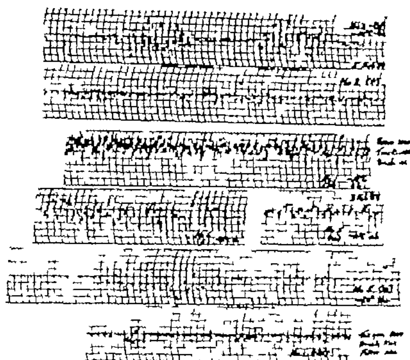


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Stevenson. In the humans, were the muscles you studied completely at rest? Was the subject lying down and relaxed?

Sellers Our subjects have all been sitting in wheel chairs, with the electrodes inserted, or attached they have not moved from a comfortable sitting position.

Stevenson Are your animals unanesthetized?

Sellers Both anesthetized and unanesthetized. Even in the anesthetized animals we customarily observed some basal activity if that is the correct term.

Burch Did the diaphragm contribute to the surface electrodes?

Sellers It certainly did not in the humans, Dr Burch, as the inactive muscle is silent.

Burch I wonder about the animals

Sellers I think in animals it depends on which muscle we choose to measure If we measure muscle activity in the upper limbs of a rat, we usually obtain quite a contribution from heart activity and probably from diaphragmatic activity If we record from the hind limbs there is no detectable contribution from the activity of the heart, but I am not sure about the diaphragm.

Burch If man is not relaxed, we have encountered difficulty with diaphragmatic activity particularly if the patient is orthopneic or has exaggerated breathing, when recording our cardiographs in our studies on the isopotential reference line or point.

Sellers In the experiments we are doing with humans, where two surface electrodes are put quite close together on the gastrocnemius the base line is completely flat

Burton Mr Chairman, perhaps I should speak on this subject, as many years ago I studied the electrical activity of shivering muscles in animals with Dr D W Bronk now Director of the Rockefeller Institute for Medical Research, and we learned a good deal about it.

For four or five years Dr R. A. Snyder now a member of the Division of Biophysics, Defence Research Medical Laboratories, Toronto Canada, has been studying, not the effects of cold and shivering and the electrical activity of muscle, but the general relationship between the electrical activity and tension, and presumably the heat, produced in muscle Dr Snyder is now studying the muscle activity in shivering humans, but the work is not far enough advanced for me to report on it as yet.

As to the position of the electrodes, I feel strongly that those physiologists are wrong who insist that one must record the single motor unit response by concentric electrodes That method can never hope to tell us anything about the activity of the whole muscle. For that, one must

use a single needle electrode stuck in the belly of the muscle, and another farther down the muscle in order to obtain any kind of sample of the activity of the whole muscle.

As to the distance apart of the two electrodes, Dr Snyder has investigated that very carefully The best representative sample, which he thinks may represent about a third of the muscle mass, is obtained if you place one surface electrode in the belly of the muscle, and the other near the tendon. We are convinced that surface electrodes give us a much better sample than concentric needle electrodes, which pick up only a few units

I think we will have to use some caution A profitable field for members of this conference to investigate would be the electrical activity of muscle, but I would warn you that there are many other factors quite unsuspected by physiologists, or even by electromyographers

As to the relationship between the electrical activity put out by a muscle, which we usually integrate there are technical difficulties with the frequency response of the integrator it must be very flat and cover a large range. In a given muscle at a given time, the integrated electrical activity bears a very nice relationship to the load, or to the tension exerted by that muscle. The shape of the curve relating the integrated electrical activity to the tension is characteristic of that particular muscle

The flexor muscle in my left arm gives a slightly different curve than the right, and we can tell by looking at the records which arm it is This can be interpreted, we think, in terms of thresholds of the motor horn cells in the spinal cord. But the striking thing is that, when we go from one subject to another we find that one subject, in lifting the same weight, will produce only perhaps a third of the integrator electrical activity in his biceps muscle as does another

This difference is related to the maximum strength of the muscles. Admittedly it is difficult to measure this strength because psychological factors play such an important part, but one can try by measuring the maximum load he can lift The people who have strong muscles in their arms produce much less electrical activity in lifting the same weight than those who have weak muscles

Horwith Isn t that partly due to the fact they bring in other muscle groups to supplement it?

Burton. No we have tested that by recording from the supplementary muscles but because of the way in which the experiment is done, I think we cannot use these muscles very effectively anyway

The differences between subjects are due apparently to the basic fact that the electrical activity is something physiochemical coming from the surface of the muscle whereas the total tension, and I should think

the total heat produced, is a function of the volume of sarcoplasm. When a muscle is developed by training, or is normally stronger than a similar muscle in another animal, we have a greater volume of sarcoplasm in each muscle and it produces more tension, but it does not provide correspondingly more electrical activity.

Dr. Snyder did some experiments on himself by lifting bar bells for six weeks and he was able to increase the maximum load of the arm by 25 per cent. The diameter of his arm increased, but the electrical activity did not increase at all, which would confirm the impression we have had. There is an excellent correlation among the biceps muscles of medical students, between the total load, and the ratio of electrical activity to load.

I should like to introduce a word of caution as to the complication which comes in when we use this method to assess the muscle activity from animal to animal. It seems to me we might find an animal that gave out only half the electrical activity of another, even though the muscles were producing just as much heat.

One also has to ask the question whether the acclimatization may not have produced some change in the muscle, so that the electrical activity again deceives us as a measure of the heat produced. I am not sure that these things are significant, but I think they should be investigated.

Stevenson: When, for any group of subjects, one obtains the maximum load each one can lift, does that produce more or less the same electrical activity?

Burton: Yes, it is much more constant than the maximum load itself. As you know, if people really want to lift a bit more, they will. It is not an accurate physiological measurement, because of psychological factors.

Burch: I agree with Dr. Burton. If the cardiac muscle is an index of the situation for skeletal muscle, there is no doubt that the electrical activity of the cardiac muscle, as recorded on the surface of the body in manifested potential variations, does not correlate with the work output of the heart. Furthermore, the recorded potential is influenced by the fields around the source of the potential, so that if there are variations in the field due to edema, fat, or shape of a part such as the heart, there may be considerable variations in the manifested electrical potential.

Burton: The best example would be *pulsus alternans* where the mechanical output of the heart alternates but the electrical voltage is exactly the same in each.

Burch: In *pulsus alternans* it is the other way. Electrical alternation may correlate with mechanical alternation.

Ferrer: Not always, as there may be no electrical alternation at all in presence of *pulsus alternans*.

Burch That is true electrical alternation does not always correlate with the mechanical alternation because sometimes the maximum electrical output may be associated with the weakest beat

Belsake The correlation may be between electrical activity and oxygen consumption. What is the energy required to lift these weights?

Burton. We have not done that. In the work I did with Dr Bronk, years ago we found that in cats an increase of oxygen consumption was coincident with the first electromyographic indication of an increase of electrical activity We never found any increase of oxygen consumption in response to cold that was delayed or occurred sooner than did the start of the electrical activity

Sellers At that time visible shivering was not present

Burton: There is a long process before we observe visible shivering the units are initially out of phase and out of frequency with each other and it is only in the end stages that it appears I think we must discard it as a measure of activity of the muscle.

Sellers. As you know our work has completely confirmed your observations with Dr Bronk. In a study such as yours, or our recent ones, if there are electrodes in place in muscle, and the environmental conditions are altered, I think, in spite of what Dr Burch has cautioned us about, that an increase in electrical activity of the muscle would indicate that a change is produced by variation in environmental conditions

Burton. It may not necessarily be an increased activity of the muscle It might be a change in the electrical conductivity of the skin, might it not? It indicates a change, caused by say the acclimatization, but not necessarily taking place in the muscle itself

Sellers. Even with needle electrodes, Dr Burton?

Burton. By needle electrodes, do you mean single needle electrodes, not concentric ones and measuring single units?

Sellers I shall make the matter more specific In our experiments on rats, we put a safety pin electrode right through the muscle the pin of the safety pin is uninsulated, so we are recording along its whole length. I should think an alternation in the electrical activity caused by an environmental change would, in all probability indicate a change occurring in the muscle

Burton It is not necessarily an increased tension and activity of the unit. The conduction, the spread of the field, is a very important factor indeed in what is recorded.

Burch I agree with Dr Sellers that if the electrical activity is increased, the mechanical activity of the muscle is also increased. I merely wished to introduce a word of caution regarding the lack of absolute direct quantitative relationship of electrical activity to heat production

Certainly the muscle must be producing more heat with more active electromyograms

Behnke Dr Carlson, what is the oxygen consumption in conjunction with these electrical records?

Carlson I do not have the data for that. One could only assume that our calorimetric data would apply and that two animals were virtually the same after two hours

Sellers We have done that, Dr Behnke. While the errors in estimation of oxygen consumption are increased by the technical difficulties of making muscle measurements there is no doubt that the oxygen consumption increases concurrently with the increase in electrical activity of the muscle. There is *no great difference in the immediate response* of the acclimatized or nonacclimatized animal. I think that is shown in Figure 5

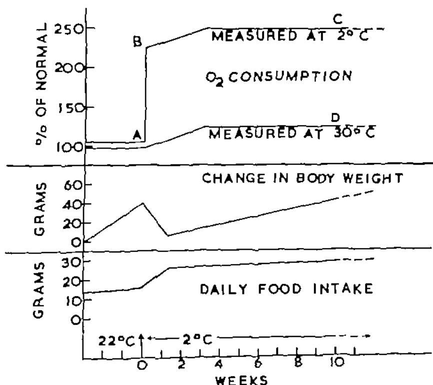


FIGURE 5 A composite graph to illustrate changes in oxygen consumption, body weight, and food intake observed in rats of about 180 gm. on exposure to 2 C. The summed electrical activity of skeletal muscle is greater at point *B* than at *A* is greater at *C* than at *D* is less at *C* than at *B* and is less at *D* than at *A*.

Bebnke The total electrical activity was greater or equal to that of the acclimatized animals in Dr Carlson s experiments.

Sellers The total activity of the muscle?

Bebnke In the integrated record of Dr Carlson, what was the summation of the electrical activity in the acclimatized rabbits or rats compared with nonacclimatized under the conditions of cold?

Sellers Whether the animal is acclimatized or not, when it is placed in a cold environment, its muscle activity goes up That is indicated in Figure 5 where the muscle activity at point *B* is greater than at point *A* The upper line indicates the rate of oxygen consumption.

I agree with Dr Carlson s data, that during the first week or so of exposure to a temperature of 1 C. or 2 C., there is a further increase in the total oxygen consumption of the animals in the cold, if they are measured at that ambient temperature However some of this is not in complete agreement with Dr Carlson s data, for if the measurements of oxygen consumption are carried out at 30 C., there is an increase in oxygen consumption which occurs gradually and amounts to about 20 to 25 per cent. Once it has reached that higher level, if the animals are kept in the cold it remains more or less constant. There are some slight variations but these are not significant, however long the animal remains in the cold.

After a certain length of time these animals can be considered to be acclimatized, and if the muscle activities are taken then—and I am speaking of integrated activity—it is found that the muscle acti ity of an acclimatized rat, measured at 30 C., is less than that of the control unacclimatized rat measured at the same temperature. It is found that the muscle activity of the acclimatized rat measured at the cold temperature, is less than the activity of the nonacclimatized rat measured at the same temperature But there is always greater muscle activity at low than at high temperature. Does that answer your question completely?

Bebnke Yes I was wondering what the correlation was between oxygen consumption and the electrical activity of the muscle

Sellers I cannot give it to you in mathematical terms.

Bebnk With egard to basic work on this subject, I can cite an experiment that does not have anything to do with cold but with the basal metabolism of an individual, in which electrical recordings were made of the muscles of the thigh and the biceps. The oxygen consumption per minute in a control test was 256 ml in several successive runs, during a period lasting about an hour and one-half Then, when the bead pillow was removed (that is the only thing that was done) the body muscles were under slight tension and the corresponding electrical activity was greatly increased. Oxygen consumption increased from 256

to 295 ml. per minute. I believe one can quantitate this electrical activity in terms of oxygen consumption.

Sellers I think there is no doubt about that. However we have had a harder time in our human experiments which are not yet complete, in ruling out extraneous factors or controlling them satisfactorily

In our experience, if animals are removed from a cold environment, the metabolic rate falls more quickly than the rate of increase observed when the animals were first placed in the cold. Measurements carried out at 30 C., take from one to three days, and the measurements remain variable for another couple of weeks.

Horvath Doesn t even one day of exposure result in some of that increase, and isn t there a considerable variation in time? That is what we found

Sellers Yes this agrees with your work pretty well. There is a change even after one day After four or five days we cannot measure a statistically significant difference from the normal oxygen consumption of a rat of that particular size.

The other information given in Figure 5 is very similar to that presented by Dr Carlson. Before exposure to cold, the change in body weight is represented by a curve in the lower half of the figure when the animal is placed in the cold room there is almost always a loss of body weight which usually lasts for about a week, and then the growth curve, as represented by an increase in body weight, proceeds at a slower rate than before exposure to cold. In other words, the growth rate, in our experience is always somewhat slower in the cold. I think that finding agrees very well with those of Dr Carlson, Dr Dugal and others who have worked in the field

Horvath Isn t the growth rate slower anyway after a period of a couple of weeks After all the growth rate curve is not a straight forward indefinite progression, and as these animals become older there is going to be a decrease in the growth rate Does your growth curve follow the ordinary decrease or is that a different decrease?

Sellers That is a different decreased rate If control animals are kept at 22 C their growth rate curve might continue going up for a considerable time before forming a plateau. In the cold there is a gradual attainment of a plateau, but it takes a much longer time than at room temperature.

Carlson They do form a plateau at a lower level, in terms of body weight.

Sellers I think you are right, Dr Carlson

Dugal Dr Sellers, you said that when a rat is placed in the cold

room, there is a loss of weight that lasts for about a week? That would depend on the initial weight, and on the temperature used, would it not?

Sellers The ambient temperature and the weight of the animals which are put in the cold environment certainly influence the change that takes place.

In Figure 5 I ha e represented this, for purposes of discussion, as an average finding of a rat of average weight.

Dugal What do you call average weight for a rat?

Sellers We used rats from 180 to 200 gm. in most of this work. In our experience, a rat that is placed in the cold room, weighing about that amount, will lose less weight than a rat during the more active growing period when it might weigh 140 gm., for instance.

Horvath What happens to the growth curve of the rats after being taken out of the cold completely and put back into say 22 C? Do they resume their normal growth curve and attain the same weight they would have attained if they had not been exposed to the cold?

Sellers We have done that experiment Apparently the result is much the same as when an animal is put on some adverse diet. The growth curve, after the removal from the diet or from the cold, parallels the growth curve of control rats that never received the adverse diet or were never placed in the cold.

Blair We answered Dr Horvath s question somewhat by accident down at the Fort Knox laboratory when we were acclimatizing rats to a cold environment of −5 C. We had at first acclimatized rats weighing about 350 to 400 gm., to cold. Then we received a new shipment of rats to be acclimatized under the same conditions They were much smaller 175 to 200 gm., and when put under identical cold conditions not harmful to the larger rats they began to develop cold injury of the feet, ears, and tails after a few days of exposure. The experiments had to be discontinued and the rats returned to room temperature. After several weeks at room temperature these rats showed the same growth pattern and body weight as the rats that had never been exposed to cold.

As Dr Sellers stated the response to cold, in general depends upon the age and body weight of the animals that are used. We cannot standardize the procedure for a 350 gm rat and expect the same principles to hold true fo 150 or 250 gm. rats Different procedures must be used

Pagé I think it is even more difficult than that We found that when exposing rats of the same average body weights to the same temperature at the same season of the year we obtained different responses. Some times they required four months to recover their original body weights, and sometimes two months, in spite of ha ing the same dietary history

It is a bit unpredictable. The best thing we can do is to use animals of the same weights but that does not rule out any chance differences.

Blair We assumed that rats of the same strain, and grown under identical conditions, would have approximately the same body weight at the same degree of maturity that is until they reached a growth plateau at which there was no further increase in body weight with advancing age.

Sellers We have had the same difficulty that Dr Pagé described. Sometimes there will be a much greater loss of weight, and a slower recovery period than others I do not know how to explain it It certainly makes the assessment of any results, especially those on nutritional subjects, most difficult.

Dugal Did you notice any difference in loss of weight during exposure to cold, between large rats and small rats? We found that young growing rats weighing around 60 gm lose very little weight and for only a day or two when exposed to a temperature of 2 C. whereas adult rats weighing 200 gm., as you have just said, lose weight at 5 C. for about a week.

Sellers I think that is right although most of the rats of 60 gm. or thereabouts, when put at a temperature of 1 or 2 C., do not survive. There have been exceptions, but the survival rate is much lower in rats of that age and size.

In our experience, the food consumption shows the same changes that have been pointed out by Dr Carlson. there is a gradual increase in food consumption over a period of a week or so, perhaps a bit longer but then the food consumption remains at the new high level, and gradually increases concurrently with the increase in body weight.

The changes in the endocrine glands had been studied by other people before we became interested, notably by Selye (21) in the case of the adrenal and Horvath (18) in the case of the thyroid. Much earlier in 1916 Cramer (22) reported the hyperplastic change in the thyroid during exposure to cold Our findings are much the same as those of the other groups.

The adrenal becomes larger very quickly and remains so throughout the entire period of exposure After 18 months, if we kill a rat, its adrenals are still very much enlarged. The thyroid becomes hyperplastic within the first three weeks, and probably reaches its greatest state of hyperplasia at about this time. During this period, as others have reported, the uptake of radioiodine, whether you measure at two hours or twenty four hours, is considerably above the control rate

If we observe the thyroid over a very long period after a year or so we find that the gland has decreased somewhat in weight, relative to

body mass, and involution has occurred. However in my opinion, there are areas which are still hyperplastic interspersed between apparently inactive areas of the gland. Measuring protein-bound iodine and iodine uptake in very long-term experiments we find that the results differ considerably. Sometimes there appears to be a greater uptake than in normal animals, but sometimes there does not.

The same is true for the PBI. Usually it is slightly elevated, in our experience but not very much. The responses are influenced greatly by the amount of iodine in the diet, and we are planning to extend our observations under conditions of controlled iodine intake. I think we can say that the variations in iodine uptake, and in plasma protein-bound iodine, are greater than in the normal after chronic exposure.

Now all these changes, to my mind, indicate that some change has been produced in the tissues themselves by prolonged exposure to cold. There are some additional reasons which we have advanced to demonstrate that there are tissue changes.

The changes that take place in the tissues of rats exposed to cold are an increased oxygen consumption and activity of succinoxidase. These have been shown in *in vivo* studies in the Warburg apparatus. These increases can be shown in the case of liver, kidney and adrenal. Table II illustrates the actual figures obtained in some of the *in vitro* studies of oxygen consumption in liver slices of rats exposed to a cold environment. The differences observed are about 30 per cent. They vary a little depending upon the way they are expressed.

Crismon: Were these QO_2 values corrected for glycogen?

Sellers: These particular ones, I believe, are expressed per milligram of dry tissue. If they are expressed per milligram of nitrogen, the differences become slightly greater, but that is correct for glycogen.

Dr. Kurt Weiss (23), while in Dr. E. F. Adolph's laboratory at the University of Rochester, confirmed the increase in oxygen consumption, and extended the observation to include heart muscle. Our work on skeletal muscle tissue has been somewhat difficult to interpret. Dr. Dugal has made a study of this and I shall ask him to continue the discussion.

Dugal: Dr. Desmarais (24), in my laboratory at the Laval University, has studied the chemical activity in the psoas muscle of rats acclimatized to cold, as compared to that of rats kept at room temperature. Using the method of Perry and Cumming (25), which allows us to follow the succinic dehydrogenase activity, he found that activity to be the same for the muscles of rats being adapted to cold, and of controls kept at room temperature. However he found an increase in the adrenal activity under the same conditions and with the same method. I think those

TABLE II

Succinoxidase Activity of Livers of Rats Exposed to Cold (2 ± 1 C.)
(QO_2 = c. mm. of Oxygen Uptake per mg. of Dry Tissue per Hr at 38 C.)

	Cold				Normal			
Days of Cold Exposure	Sex	Body Wt gm.	Liver Wt. gm.	Succinoxidase QO_2	Sex	Body Wt gm.	Liver Wt. gm.	Succinoxidase QO_2
27	M	235	14 10	85 0	M	240	10 30	56 1
28	F	200	10 4	100 0	F	240	9 55	63 1
35	F	190	11 65	102.0	F	196	8.25	65 1
37	F	182	11 50	82.5	F	220	10 55	68 0
41	F	196	8 70	78.2				
42	F	165	8 05	110 0	M	165		57 0
42	F	205	9 95	86 6	M	170	10.00	56 5
47	F	200	9 45	104.2	F	250	9 75	66.8
47	F	195	8 50	98.2				
70	F	225	9 70	107 0	F	230	7 00	71 5
Average				95 4 ± S. D 11 3	Average			63 0 ± S. D 5 9

Reprinted, by permission, from You, R. W and Sellers, E. A. Increased oxygen consumption, and succinoxidase activity of liver tissue after exposure of rats to cold. *Endocrinology 49 374 (1951)*

results fit nicely with yours, even if Desmarais results are measured only according to wet weight.

Sellers In the increases I have just mentioned in adrenals and kidneys, whether the value is calculated according to wet weight, dry weight, or nitrogen content of the tissue, there is an increase, usually of the order of 20 per cent.

If we remove insulation from the animal by removing its fur as one would expect the metabolic rate goes up considerably That is indicated in Figure 6. As a matter of interest, if the oxygen consumption of these

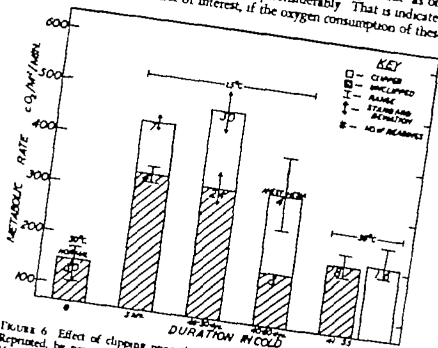


FIGURE 6 Effect of clipping upon the metabolic rat of rats exposed t cold Reprinted, by permission, from Sellers, E A Reichman, S Thomas, N and You, S S. Acclimatization to cold in rats metabolic rates *Am J Physiol* 167 651 (1951)

same clipped rats is measured t 30 C the values obtained are of the same order as those of rats that have not been clipped

This illustrates the great increase in metabolic rate that occurs when the insulation is removed and the rapid fall that occurs when such animals are anesthetized with pentobarbital In our experience, if the nesthesia and the measurement are carried out in the cold room, the animals do not survive the stress of anesthesia superimposed on the cold

temperature, but I am sure this could be altered if the conditions were varied somewhat I am speaking only of the one temperature, from 1 or 2 C. The rate of oxygen consumption (under anesthesia) is higher for an adapted rat than for a nonadapted control It is tempting to suggest that increased metabolic activity of visceral tissues in the case of the adapted animal is responsible for the difference.

In Table III we see another reason for believing that a change takes place in the tissues themselves during acclimatization. Some older work

TABLE III

Effect of Acclimatization on Survival Time of Rats in a Cold Environment after Adrenalectomy
(Exposure to Cold 3 Hours after the Operation)

No of Rats	Sex	Av Body Weight (gm)	Duration in Cold Before Adrenalectomy (Days)	Survival Time (Days)	
				Av	Range
8	M	269	63 109	12	4 5 30
8	F	164	91	12	4 5 16
5*	F	192	91	>30	
13	M	221	0	2 4	0 5 3
10	F	214	0	2 4	0 5 6

All drenalectomized rats given saline *ad libitum*
Sham operation

Reprinted, by permission, from Sellers, E. A You, S S., and Thomas, N. Acclimatization and survival of rats in the cold effects of clipping, of adrenalectomy and of thyroidectomy *Am J Physiol* 165 481 (1951)

on the effect of adrenalectomy is illustrated here If an adrenalectomized rat that has lived in the cold room before the adrenalectomy is then placed again in the cold environment it will live for a longer period than an adrenalectomized rat which has not been kept in the cold room prior to the adrenalectomy I am not clear on the reason for this, except that I think it indicates the tissues themselves must have been altered in some way

The same thing may be demonstrated in the case of thyroidectomy as shown in Table IV The point is exactly the same, that if an acclimatized

TABLE IV

Effect of Acclimatization on Survival Time of Male Rats in a Cold Environment after Deprivation of Thyroid Function

No of Rats	A Body Weight gm	Duration in Cold Before Thyroidectomy (Days)	Thyroidectomy	Survival Time (Days) A	Range
12	216	0	Surgical	7.8	5-12
7	201	75 78	Surgical	34.6	19-43
8	171	0	PTU*	8	7 10
10	181	25-141	PTU*	24.8	19-38

*Propylthiouracil 0.05 per cent in diet

Reprinted, by permission, from Sellers, E A, You, S S and Thomas N Acclimatization and survival of rats in the cold effects of clipping, of adrenalectomy and of thyroidectomy *Am J Physiol* 165 481 (1951)

rat is thyroidectomized or fed propylthiouracil, it will live for a considerable period in the cold room (in this case somewhat more than a month, on the average, with quite a wide range) compared with the survival time of a thyroidectomized animal which has not been acclimatized On the average, in this particular experiment, the survival time of the nonacclimatized thyroidectomized rat was about eight days. I think it is important to note that eventually all these animals died if their thyroids were taken out. In fact they all died within six weeks or so That indicates to me that some thyroid hormone is necessary for survival, at least at this temper ture and the same can be said in the case of the adrenal These glands are necessary for the development of acclimatization

In other experiments we showed that if a small amount of thyroxin (2 5 micrograms dl-thyroxin, which is probabl about half the daily estimated requirement of a at for thyroxin) were given to rats every day they lived just about as well as the controls They demonstrated the same increase of oxygen consumption (measured at 30 C) which was seen in the controls So presumably as long s small amount of thy oid is available to the animal, t may develop a deg ee of acclimatization

Horvath The same is true f the ad enal If we take out one adrenal and lea e the other one in, the animal survives

Sellers It may be demonstrated by giving a small amount of adrenal cortical extract

Figure 7 illustrates a section of the liver of a rat which has been fed a diet low in choline for nine weeks You can see that the liver cells are filled with a large amount of fat stained red. If a similar animal is fed the same diet, and is placed in the cold, he eats about 50 to 75 per cent more than the control animal kept at room temperature, but at the end of nine weeks instead of the appearance we have just seen, the liver looks almost normal (Figure 8)

We recently demonstrated that in this type of experiment there is an increase in choline oxidase in the liver tissue. Whether this increase is merely another enzyme that shows an added activity or whether there are a few enzymes in these tissues that are specifically or partially affected by the cold I do not know nor do I know the significance of the fact that we have seen this increase in choline oxidase.

Barch Do you know whether any of the adrenal hormones will alter the fatty liver produced by choline-deficient diets?

Sellers Quite a number of people have done experiments on that. There is evidence (26) that there is an increased deposition of fat in the liver when cortisone or cortical extract is given concurrently with a diet low in choline, although the kidneys are partially protected by cortisone and the typical renal lesions do not develop I do not think anybody has ever explained that very well

Pagé What was the protein content on the choline-deficient ration?

Sellers The total protein content was about 20 per cent, Dr Pagé except that methionine was the only amino acid that was deficient. The other essential amino acids were present in amounts estimated to be adequate.

Pagé I was wondering whether the excess of intake in the cold would supply the additional methionine sufficient to produce this picture we see here

Sellers Because the animals took more food?

Pagé In absolute quantities they would ingest more methionine

Sellers We estimated the amount of methionine the animal would receive and it worked out to be somewhat less than his daily estimated requirement at room temperature But, in any event, judging from most nutritional experiments, if the food intake goes up the amount of essential amino acids that have to be taken in must go up too, to prevent signs of deficiency Usually a greater intake of an hypolipotropic diet results in more prominent signs of choline deficiency

Shumacker Dr Sellers, when you spoke about an increase of about

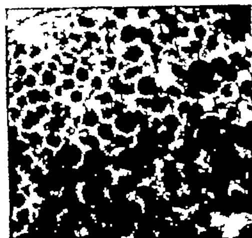


FIGURE 7 Photomicrograph from liver of rat fed low-choline diet at room temperature for nine weeks. (Approximately 220 X)

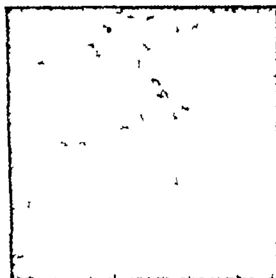


FIGURE 8 Photomicrograph from liver of rat fed same low choline diet for nine weeks at 1 to 2 C. (Approximately 220 X)

25 per cent in your studies, was that true in [illegible]
you studied or were there specific tissue diff[illegible]

Sellers In measurement of oxygen consum[illegible]

Shumacker Yes

Sellers There is a difference from tissue t[illegible] her offhand the precise figures for each tissue. O[illegible] these experiments is to know what basis t[illegible] se or nitrogen. I do not think there is any satisf[illegible] one knows which is the most applicabl[illegible] the water content of muscle, or of any [illegible] these [illegible] findings greatly

Shumacker Have you or Dr Ca[illegible] done [illegible] ture measurements of different parts of the b[illegible] ments? The reason I ask is that I believe that D[illegible] P[illegible] (27) in acute experiments on anesthetized do[illegible] temperature decreased approximately 5 C[illegible] perature. If that is true it might be of some [illegible] to the difficulties which may arise when a [illegible] surgical adjuvant.

Horvath. We have been taking those measur[illegible] so great a differential Actually the highest ten[illegible] the hepatic venous blood. In these colder animals [illegible] degrees higher than the temperature of the rectum The [illegible] ture in the heart, right heart or left heart is exactly the same w[illegible] or minus one-tenth of a degree centigrade Th[illegible] think, may be that the coronary blood tempe[illegible] different. Of course it is not too easy to cathete[illegible] in some of the cold preparations it is bad enough in the normal [illegible] tainly we find in normal animals that the temperat[illegible] of the [illegible] sinus blood is higher than that of the rectum by [illegible] rying amount I[illegible] the cold, we have had little success with them

We have catheterized about 200 dogs where we have had temperatures in the right heart, rectum, splanchnic and other areas of the arterial and venous return, and I have yet to find in any case that the temperature of the heart is much different from that of the rectum, that is at equilibrium times. The pattern of change is quite different I would not care to go into that because our own analysis of the data is far from complete.

Shumacker The experiments to which I referred were acute experiments and would reflect the changes during cooling rather than the ultimate results.

Horvath. Acute experiments are difficult to evaluate in terms of these

temperature changes. But at a stable point, where they are in equilibrium, there is certainly no difference between the temperature of the heart—whether we speak of heart muscle or heart blood—and the temperature of the rectum If we had a temperature around 22 C. in the rectum, the heart temperatures were, roughly about 22 C. also It is never higher or lower than that.

Sellers I would agree with that, judging from the sporadic work that our group has done in that field.

Horvath In the acute stages they may be quite different I do not trust the data we have obtained in such cases There are other problems of cardiac arrest occurring for a short period of time, fibrillation, and that sort of thing, which would alter the temperature measurements

Shumacker If such changes occur with cooling, I was wondering whether they might be of importance in the etiology of ventricular fibrillation which, as you know is one of the hazards associated with acute hypothermia.

Horvath We have been trying to answer that problem but have not succeeded as yet.

Burch Dr Sellers, when the animals were moved into the cold, did you change the diet?

Sellers We have done a lot of variations of that experiment In the one I showed, the animals were started on the low-choline diet the day they were placed in the cold. In case that procedure affected the results, we have also tried the effect of cold on the removal of fat from the liver by feeding a low-choline diet for variable periods before putting the animals in the cold room, and seeing whether the fat then disappeared. It appears that there is some decrease in fat content, but the experiment is not satisfactory because if an animal has the amount of fat shown in Figure 7 about 30 per cent his general condition has deteriorated and his resistance to the cold is less than that of the normal

This effect, which I think illustrates a change in metabolism of fat in the body is a matter of degree In the experiment I referred to a few minutes ago the amount of fat was 20 per cent. If the content of fat is increased to about 30 per cent we find that in the animals kept in the cold on this high-fat low-choline diet, there is a deposition of stainable fat in the liver but it is always much less than the level found in controls kept at room temperature.

I think in the experiment I have just cited, the animals being given the high-fat low-choline diet in the cold had an average of 12 per cent fat in the livers, and the animals kept at room temperature had 32 or 33 per cent fat, on the average.

Burch In the two sections you presented, what was the difference

between the two experiments? In the first one, you fed the choline deficient diet at room temperature. What was given in the second?

Seller The animal in the second experiment received exactly the same diet but, the rats were exposed to temperatures of 1 to 3 C instead of being maintained at 22 C.

Burch You prevented the development of the hepatic alterations, but you did not cure the hepatic disturbances

Sellers That is preventive not curative

Horvath Did the animals on the low-choline diet survive better or less well than those fed on the normal diet?

S llers They did not survive better than the animals on the normal diet, but did better than those on the choline-deficient diet at room temperatu e The survival rate was about the same as in rats fed a normal diet kept in the cold

We tried to produce cirrhosis in the cold by feeding this same low choline diet but, as you would guess, it does not occur because the animals never ha e enough fat in thei livers to develop that type of cirrhosis. So in spite of the fact that we kept them in the cold for s x months, giving a diet low in choline there were no signs of cirrhotic processes.

H rvath They did survive six months, though

S llers Yes.

Pag You think that implies increased fat utilization

S ller I think it illustrates either (*a*) that in the cold, choline is not necessary for the metabolism of even larger amount of food than the nimals eat at room temperature, or (*b*) that choline is utilized more efficiently I think it suggests that there may be a difference in the utilization of fat in the cold Although in other experiments where we ha e attempted to demonstrate a difference in survival rate and growth te dependent on the content of fat in the diet (which v ried from 6 5 per cent to 41 per cent) we could find no convincing evidence that the animals receiving the high-fat diet did much better than the animals receiving low fat diets The intake of food on the various diets depended lmost completely on aloric value of the diet, not the content of fat

If an inert material like cellulose was placed in one of the diets it ppeared to affect the pal tability of the food The c loric v lue of the diluted diet was less than that of a diet not containing cellulose and therefore the grow th rate was less although in this particular experiment there w s no definite effect on surviv l

I do not feel that those experiments demonst ate that f t is not ut lized better under some cumstances n the cold I think it importance may not be as great as we have thought in the past and that caloric intake

is the most important factor governing the amount of food that is consumed. But I would not rule out the possible importance of fat under some circumstances. Of course, the weight of diet is much less if the content of fat in it is high, because the caloric value per gram is so much greater.

Horvath. Does the amount of fecal fat vary in these animals? After all, if greater intakes are given, the amount of fecal fat increases quite markedly. What about the animals that were in the cold, with the low choline-high fat diet, and the amount of fecal fat that they had in their stools?

Sellers. We did not estimate that, Dr. Horvath.

Stevenson. If we put animals on a high-fat diet made isocaloric by weight with a high-carbohydrate diet, they usually eat the same number of calories.

Pagé. On a high-fat diet, the caloric intake is larger and they will deposit more fat at room temperature.

Stevenson. If we put them on an isocaloric high-fat diet in the cold, they will eat the same quantity as on other diets and gain weight as well, so they cannot be losing much in the stools.

Horvath. Isn't it generally true that the more fat in the diet the more fat in the stools?

Brown. Not in man.

Pagé. I have never heard of that.

Sellers. Dr. Pagé, do you think a high fat diet is utilized better in the cold than it is at room temperature?

Pagé. I think it is about the same. Forbes and his co-workers (28) have reported that raising the fat content of the ration increases the efficiency of food utilization. We have found this increase to be the same in the cold as at room temperature. It may be more evident in the cold because of the larger food intake.

Burch. Has anyone measured the pancreatic activity on high carbohydrate and high-fat diets?

Sellers. I am sure that has been done.

Burch. In the cold?

Sellers. I do not think anyone has reported data on pancreatic activity in the cold. We have measured insulin content, islet volume and pancreatic weights in the cold on one ration only, the controls being kept at room temperature. This was done in collaboration with Dr. R. E. Haist and Mr. Donald Baker.

There is an increase in the weight of the pancreas in the animals kept in the cold. The alterations in islet volume and insulin content of the

pancreas are not very great, but the results are being analyzed for significance at the moment.

To sum up: On exposure to cold there is an immediate increase of oxygen consumption which I attribute, as many others have done before me, to increased muscle activity that is not necessarily associated with visible shivering. During the succeeding couple of weeks, there is a further increase in oxygen consumption which Dr. Carlson has shown directly and it occurs concurrently with the increase in oxygen consumption observed when the measurement is carried out at 30° C.

I attribute this change to an increased rate of oxygen consumption by the visceral tissues, and as you may remember this has been demonstrated *in vitro*. The liver, I believe, plays an important part. The kidneys play some part, and I should suspect, from Dr. Pagé's data, that the intestine also may be concerned with this raised basal metabolic rate.

I believe that the changes in the visceral tissues are very likely influenced by increased activity of the thyroid, which you will remember also is most hyperplastic and shows its greatest enlargement about the same time. The maximum is reached in about three weeks. I think the adrenal cortex also plays a part in this increased visceral heat production. There is additional evidence that the two glands act in concert, from the fact that a type of "acclimatization" may be produced by feeding thyroid substance and adrenal substance, cortisone, to animals for a week or so before putting them in the cold room, and thereby increasing their resistance to cold.

If muscle activity is measured after acclimatization has been produced, it is less active than in the case of the same rat immediately on exposure. I would suggest as a likely hypothesis that the increased visceral production of heat makes the muscle activity less necessary for maintaining the body temperature at a normal level. If the ambient temperature is lowered, when the animals have been acclimatized to a temperature of 1 or 2° C., we shall again see an increase in activity.

I suggest that muscle activity could be regarded as a means of producing heat quickly, which becomes less necessary as visceral heat takes over the heat production. I think that increase in visceral heat production explains the increase in total metabolic activity that occurs during acclimatization. I also believe that it explains why it is possible to lose more heat from the surface of the body in acclimatized animals and still successfully maintain the core temperature.

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METABOLIC STUDIES OF THE ESKIMO*

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IN 1947 THE FIRST group from Queen's University went to the Arctic, and since then there have been trips in the summers of 1947 1948 1949 and 1950 there was also one winter trip in 1949 The summer trips, and the one winter trip were to Coral Harbour Southampton Island, Northwest Territories (see map frontispiece) and in 1949 the group also went to study a much more isolated group of Eskimos at Igloolik Island, in the Straits of Fury and Hecla, Northwest Territories There have also been experiments both with men and animals carried out in Kingston Ontario in an attempt to elucidate the meaning of some of the data we have obtained on the Eskimos.

Our work has been chiefly concerned with the effects of cold, but it is obvious that an important factor to be born in mind when considering any of our data, is the peculiar diet of the Eskimo which diet is the result of his peculiar environment and the foods which are available in it It is necessary therefore, for adequate consideration of some of the subsequent data, that the nutritional background be outlined by first outlining some of our observations on the caloric intake of the Eskimo Then I want to make some comments on their protein, fat and ascorbic acid metabolism.

CALORIC INTAKE OF THE ESKIMOS

The data in Table V concern a group of eight Eskimos who were observed during the summer During the experiment large amounts of their foods were available to them The food which they took from the cooking pots to the plates was weighed and the scraps were weighed at

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TABLE V

Daily Measured Food Intakes of 8 Adult Eskimos in Summer

	Meat gm	Blubber gm.	Bannock gm	N Excretion gm/24hr.	Calculated Protein Catabolism gm/24hrs.
Walrus Meat Period					
Family I					
Average	343	114	208	14 3	89
Minimum	150	35	110	5.2	32
Maximum	680	245	430	24 5	153
Family II					
Average	365	333	0	14 6	91
Minimum	167	180	0	8 7	54
Maximum	650	665	0	30 9	193
Caribou Meat Period					
Family II					
Average	904	35	209	22 4	140
Minimum	570	0	140	10 4	65
Maximum	1110	173	260	32.0	200

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the end of the meal. This procedure limited them to three meals a day which constituted some interference with thei natural eating habits, for they tend to dip into the pot at whatever time of the day they wish. I have said already that the experiment was carried out in the summer a time when their activity was at very low level They were brought to live in tents nea the hut in which we were living and the most energetic activity carried on by them during that period was a little ivory carving There were four males and four females, all adults, in the group Four of them were Ivliks, who had come from the western shore of Hudson s

Bay and the other four were originally from along Hudson s Straits in the East (see map, frontispiece)

The first thing apparent in Table V is the great variation in their food intake. The walrus meat period lasted three days and during that time they had access to an unlimited quantity They could choose the amount of fat or lean meat which they ate and they were also free to decide whether they wanted to make bannock.

Horvath What is bannock?

Brown Bannock is a biscuit made with flour baking powder with some salt added to it If they are flush they will use lard to make it, if not, they will use seal oil It is difficult to arrive at a reliable figure—in fact you can t—for the composition of bannock and its food value, and a conservative estimate will be used when it enters into later calculations.

As I have said, during the first three-day period they had walrus meat. During the second three-day period there was fresh caribou available and this was considered to be a treat and therefore some of their intakes were very high. For this part of the experiment, only the four Ivliks were used.

The first point to be noted then, is the great daily variation in food intake, and this is illustrated in a single individual in Table VI One man was followed for six days and his intake at each of his meals is shown. The meals which consisted of raw food when his wife did not bother to cook, are indicated. It may be seen that for three days he ate no bannock at all In addition to the foods shown in the table, these subjects also were allowed to drink tea, to which they added sugar and sweetened condensed milk. They drink large amounts ot tea and are liberal with both the sugar and the milk, so that even if they drank only three cups a day one would have to allow an extra 150 calories over and above what was recorded.

Crismon Do these Eskimos add salt to their food at all?

Brown A very small amount. A little salt goes into the bannock at times, but at other times just baking powder

Crismon Were mineral analyses made of the food?

Brown No Calculations of the observed food intake in Table VI indicate that this man s caloric intake varied from 5 400 calories on the first day to 1330 calories on the fifth day for three days there was no carbohydrate in his diet except for muscle glycogen and the sugar and sweetened condensed milk in his tea. His average caloric intake was 2760 calories, omitting the sugar and milk in his tea and over this period 23 per cent of the calories came from protein, and 68 per cent from fat. In Table VII the average diet composition in the group is as a whole shown. Generalizations about the Eskimos are to be avoided and I want

TABLE VI
Measured Food Intake for Adult Eskimo
Male Aged 45 Years 144 lbs.

Day	Meal	Type of Meat	Lean gm.	Fat gm	Bannock gm.
1	b	Walrus	75	130	0
	d	Walrus	92	145	0
	s	Walrus*	93	391	0
2	b	Walrus*	0	124	0
	d	Walrus	125	96	0
	s	Walrus	155	89	0
3	b	Walrus	98	36	0
	d	Walrus	194	90	0
	s	Walrus	112	57	0
4	b	Caribou*	302	56	0
	d	Caribou	404	0	71
	s	Caribou	405	117	117
5	b	Caribou	202	0	130
	d	Caribou	435	0	65
	s	Caribou	340	0	60
6	b	Caribou	100	0	50
	d	Seal	394	0	84
	s	Seal	186	0	79

*Eaten raw

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TABLE VII

Eskimo Diet Composition
(Average daily values)

Author	Protein (gm.)	Fat (gm.)	CHO (gm.)	Total Calories
Krogh and Krogh (1) 1913	282	135	54	2 560
Rabinowitch *et al* 1936 (5 6, 7)	250-300	150	40	ca 2 600
Høygaard (8) 1937	299	169	22	2,800
Brown *et al* (9) 1947	103	207	54.5	2,500

to emphasize that our figures represent the average observed food intake during a period in the summer when this particular group was relatively inactive. *During the three-day period, mentioned in Table V when they* were eating walrus meat, they had, on the average, 103 gm. of protein, 207 gm of fat, and 54 gm of carbohydrate. These foods gave them about 2,500 calories a day However these figures should be taken as having reference only to the group studied In the two places in the Canadian Eastern Arctic in which we made observations, we found considerable differences between groups, as well as differences between individuals and furthermore, variations in day-to-day intake in the same individual.

Coffey Do these figures all apply for the same seasonal period?

Brown Yes. They were all obtained in the summer in August 1947

The other figures in Table VII are very interesting The figures published by Krogh and Krogh (1) were really calculations based on information which was collected in the 19th century in Greenland in 185 by H. Rink (2) and in 1877 and 1900 by H Rink and S. Rink (3 4) Their object was to estimate the diet of the Eskimo before it was modified too much by the contact of the Greenland Eskimo with the Dane Rabinowitch s figures (5 6 7) are summer figures. His data are incomplete, as he himself comments. Høygaard s figures (8) from East Green-

land concern more individuals than do ours, but the supervision of food intake by individuals was not always as accurate as it might have been. They are all approximations and they should be applied only to the groups on which the data were collected.

Dugal How do your own observations during the summer compare with your observations during the winter trip?

Brown Food intake was not measured during the winter trip We know however that the nitrogen excretion was about the same during the winter as it was during the summer To the 2,500 caloric estimate of daily food intake should be added at least 150 calories for sugar and condensed milk. The figure of 2 650 calories arrived at in this way corresponds very nicely with the estimate of resting oxygen consumption that was made in these people, allowing a 15 per cent addition to the basal oxygen consumption for the specific dynamic action of food, which is a generous allowance, and adding an allowance for sedentary activity (9) The correlation between the observed food intake and the energy output measured at the same time of year and calculated from the oxygen consumption is very good

PROTEIN METABOLISM

There are several interesting points in our data on Eskimo protein metabolism (Table VIII) Their average total plasma protein level as determined by the Kjeldahl and copper sulphate methods, was within normal limits The albumen/globulin ratio was also normal with each method used Our average plasma nonprotein nitrogen concentration was rather lower than that recorded by most of the other works (10 11) who have determinted it. Rabinowitch (7) for instance found an average level which was considerably higher than 27 5 mg per 100 ml.

The average creatinine excretion in a group at Southampton Island is shown in Table IX and it will be noticed that the values are quite low For the males of the group the average level was 1 07 gm. in 24 hours, and for the females 0 70 gm in 24 hours.

Travell What was the average body weight? The output of creatinine is usually related to muscle mass.

Brown The average weight for adult males was about 140 pounds, and for adult females about 125 pounds Their low a erage body weights may ha e something to do with the low figures for creatinine excretion. However low val es are also observed in hyperthyroidism, in high protein feeding and carbohydrate deprivation, circumstances which apply here In subsequent tables there will be presented other data which are correlated with creatinine excretion, nd the low creatinine excretion for 24 hours should be born in mind when they are considered

TABLE VIII

Plasma Proteins in 37 Adult Eskimos

	Average and S.D
Total plasma protein (gm. per 100 ml)	
Kjeldahl method	7 57 ± 0 58
Copper sulphate method	7 62 ± 0 69
Plasma albumen	
(gm. per 100 ml)	
Sodium sulphate method	3 98 ± 0 67
Methyl alcohol method	3 61 ± 0 54
Albumen/Globulin ratio	
Sodium sulphate method	1.20 ± 0 39
Methyl alcohol method	1 10 ± 0 37
Plasma nonprotein nitrogen (mg per 100 ml)	27 5 ± 5 3

*S D = standard deviation

The average nitrogen excretion at Southampton Island was higher than that recorded for the experimental subjects in Tables V and VI Those subjects were pretty much at rest, whereas the subjects on whom these data were collected were at their normal activities, and taking food in their usual way All of our groups in which we have 24-hour nitrogen excretions, show a higher average level than did that first group on the dietary experiment. At Igloolik Island, where the natives still adhere more closely to the old culture the nitrogen excretion was a good deal higher There were about 400 Eskimos trading at the post and during the twelve months before we went there in 1949 the post had sold them less than a ton of flour They were a much more isolated group and the difference in their diet is indicated by the higher level of nitrogen excretion.

TABLE IX

Urinary Excretion of Creatinine and Nitrogen in Eskimos

Location	Creatinine (gm. in 24 hours)	Nitrogen (gm. in gm. creatinine)
Southampton Island		
29 Subjects		
Average	0.86	30 9
Minimum	0.24	15.6
Maximum	1 72	69 0
Igloolik		
40 Subjects		
Average	—	41 6
Minimum	—	11 2
Maximum	—	71 9

The urinary sulphate excretion was also low (Table X) When one calculates from other data the sulphate/nitrogen excretion ratio of these subjects, one finds ratios that run from 1/12 to 1/25 instead of the normal 1/4 to 1/7 We are not sure of the explanation for these sulphate excretions, which in all groups, young or old, male or female, are at the lower limit of what is ordinarily thought to be normal

Burch Were the subjects in positive or negative protein balance?

Brown At any of the times we measured it, they were in positive nitrogen balance

Burch Could that be related to the low sulphate excretion

Brown Not to my knowledge as the diminution of sulphate excretion was minimal.

FAT METABOLISM

The figures for the intake of blubber and of calculated fat indicate that the fat metabolism of the Eskimo is a pretty active affair We were particularly interested in it because of the suggested importance of fat metabolism in resistance and adaptation to cold. Such figures as we have on the intake of fat have already been presented (Tables V VI and VII)

TABLE X

Urinary Sulphate Excretion in Eskimos

Location		Total Sulphate	Inorganic Sulphate	Ethereal Sulphate
		(gm per gm. creatinine)		
Southampton Island 9 Subjects				
	Average	1 92	1 79	0.12
	Minimum	0.83	0 71	0 00
	Maximum	4 96	4.80	0 41
Igloolik 40 Subjects				
	Average	1 47	1 19	0 09
	Minimum	0 14	0 35	0 0
	Maximum	7 50	3 41	0 44

In Table XI are shown the results of some determinations of fecal lipid excretion. The first experiment was done in the winter and two groups were used. One was fed 50 gm of blubber rather than fat, and the other received 200 gm. of walrus blubber Our estimate of the fat content of walrus blubber was 83 per cent. They were fed these amounts of blubber

TABLE XI

Eskimo Fecal Lipid Excretion

Fat in Diet	Season	Fecal Lipids (gm. per day)		
		Average	Minimum	Maximum
50 gm. Walrus blubber	Winter	4 41	3 72	6.50
200 gm. Walrus blubber	Winter	5 37	3 60	8 02
200 gm Walrus blubber	Summer	4 56	1 19	8 59

for eight days and the feces were collected during the second four-day period. There was no significant difference in the fecal lipids of the two groups. In the summer the experiment was done again and only the larger dose of blubber was used. There was no significant difference from the results obtained in winter and all three average figures for fecal lipid excretion were well within normal limits. The great variation between individuals may be emphasized here again. It has been seen how much food some individuals at times consumed during the dietary experiments, but some of the subjects found that getting down 200 gm. of blubber each day for eight days was a bit of a chore. One of the young men said the only way he could get it down, even in the winter, was to go off into an unheated hut, sit down, and imagine he was out on the ice floes.

TABLE XII

Eskimo Plasma Lipid
(61 subjects)

	Average (mg. per 100 ml.)	S.D.
Total lipid	520	118
Total fatty acids	379	103
Lipid phosphorus	9.88	1.98
Total cholesterol	173	29
Free cholesterol	47.5	9.4
Free cholesterol X 100/total cholesterol	27.7	3.0
Lipid P/total cholesterol	0.72	0.09

S.D. = standard deviation

The average levels of plasma lipids (Table XII) were remarkable in some ways. The total lipid and the total fatty acid were rather low as compared to average normal figures as we know them. The lipid phosphorus (9.8 mg. per cent) was rather low too and was lower, for instance, than the level reported by Wilber and Levine (12) from Alaska. Our figures for fatty acids and total lipids were also lower than theirs. Our total cholesterol figure was also lower than theirs although the free cholesterol figure was about the same. It should be stated that these

Coffey Was the pemmican prepared the usual way? That is, was it eaten dry rather than mixed up as a stew?

Brown The subjects were allowed to eat it any way they wished They could spoon it straight out of the tin if they cared to or they could prepare it as a stew They ate a good deal of it raw We ourselves thought it was rather unpleasant when eaten stewed, without anything added to it.

HEPATOMEGALY IN THE ESKIMOS

In the course of our morbidity survey on Southampton Island in 1947 we were very much surprised to find significant hepatomegaly in a number of the Eskimos In more than one-third of those examined on Southampton Island, the liver was palpable more than one finger breadth below the right costal margin and in ten per cent of the population it was three fingers breadth or more below the costal margin At Igloolik, where there were indications that the dietary intake was rather different, the incidence of hepatomegaly was higher and the liver was larger This occurs in all groups of the population (Table XIV) It does not seem inconsistent with good health, and we know that it can disappear within a few weeks. We do not know how long it takes to develop. Looking over all the data on its incidence the only thing of significance is that it is of less frequent occurrence in young females and this was more pronounced in the group at Igloolik than it was in the group at Southampton Island, which is reported in Table XIV It was found among the Ivliks and also among those who came from the Straits (Southampton Island was completely depopulated about 30 years ago, and was repopulated by bringing in Ivliks, or walrus-eaters from the west and people from the Hudson s Straits on the east) It was found among those who had for some months been eating walrus as their chief meat and in some cases as their only food among those who had been eating seal and among those who had been eating caribou. In Figures 9A and 9B, two subjects with significant hepatomegaly are shown before and after a dietary experiment which lasted for 28 days The subjects are shown in the erect position, but they were actually examined while supine, the liver edge as determined by palpation below and percussion above was marked, and then they stood for photography There have been a large number of x ray films on these people, and there is no evidence that an abnormally low diaphragm has anything to do with the greater ease of palpating the livers Hepatomegaly has been looked for in Alaskan Eskimos, but it is said not to be present. It is also presumed not to be present in Greenland Eskimos, but on the other hand Ehrstrom (15) found in Greenland an incidence of palpable livers similar to ours. I

TABLE XIV

Table Showing the Relation Between Hepatomegaly and Other Diseases, Sex and Age

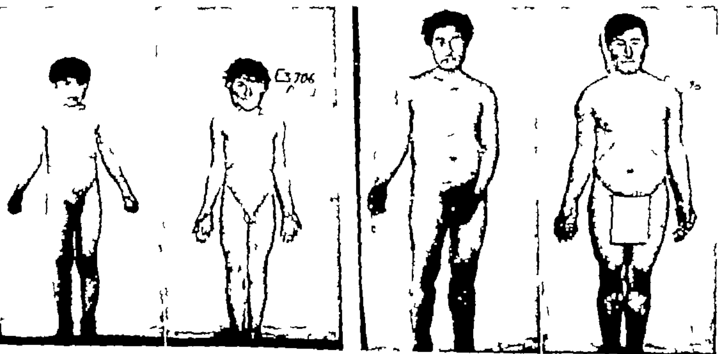
Southampton Island 1947-48

	No. of Subjects	Aged 1–10 Male	Female	Aged 11–70 Male	Female
No clinical signs of disease and no hepatomegaly	67	13	11	23	20
No clinical signs of disease but hepatomegaly	40	13	11	11	5
Clinical signs of disease but no hepatomegaly	77	5	10	31	31
Clinical signs of disease and hepatomegaly	35	9	1	15	10

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have worked side by side with those in the Canadian Arctic who did not find it until we went back over the ground and then they identified it at once

The Eskimos cooperated with us in our studies to quite an extraordinary extent, and in this particular problem to the point of submitting to punch biopsy of the liver Eight of them were biopsied at a time when they had hepatomegaly Unfortunately we have not a second biopsy in any individual after his liver had returned to normal *The sections shown* in Figures 10A and 10B, have been examined by Dr G F Kipkie Associate Professor of Pathology Queen's University and compared with biopsy material of normal livers which we have available His conclusion was that the sections were entirely within normal limits. The appearance when stained with hematoxylin, phloxine B, and saffron, is normal and fat stains show very little fat practically all of it is in a finely dispersed



FIGURES 9A and 9B. Two Eskimos with hepatomegaly before and after a dietary experiment lasting 28 days.

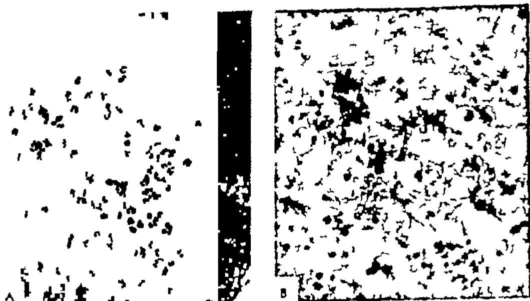
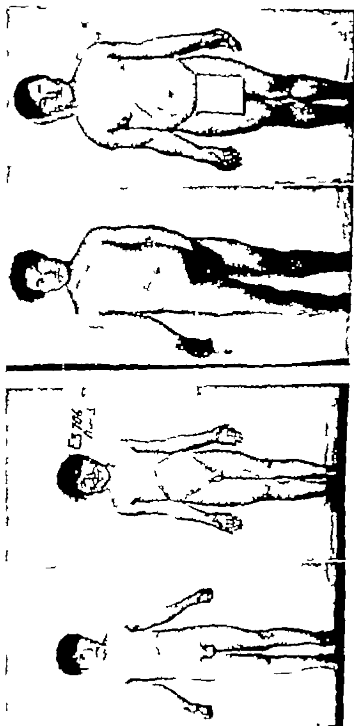


Figure 10. Sections of liver from Eskimo with hepatomegalia, obtained by needle biopsy.
A. Stained with hematoxylin, phloxine B, and saffron ×100.
B. Stained with Best's carmine stain ×600.



Pictures 9A and 9B. Two Eskimos with hepatomegaly before and after a dietary experiment lasting 28 days.

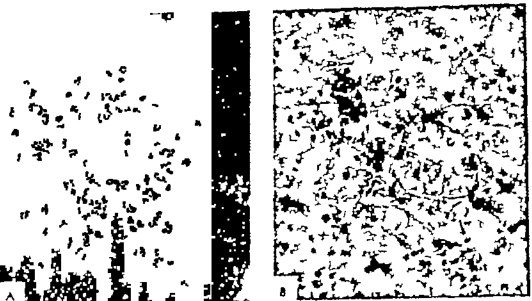


FIGURE 10 Sections of liver from Eskimo with hepatomegalia, obtained by needle biopsy
A Stained with hematoxylin, phloxine B and saffron 100
B. Stained with Best carmine stain 600.

state. There is no histological evidence of fat accumulation which could account for the increase in size that we have seen. In addition to the fat, there is a pigment present, the nature of which we do not know. It is of a brownish color which does not take iron stains and is dispersed throughout the cells. Stains for glycogen show the cells to be well filled with glycogen, but not more so than the biopsy material from normal subjects.

Ferrer: Was there any splenomegaly in these subjects?

Brown: No, there is no splenomegaly and no evidence of portal hypertension, or previous history of jaundice. The average serum bilirubin in these people was the same as it is in the rest of the population and was within our own normal limits.

A great deal of investigation has been done on the Eskimos showing hepatomegaly. As can be seen in Table XV, the subjects with hepatomegaly showed the same average levels of plasma proteins, plasma N.P.N., plasma lipids, serum calcium, serum phosphorus and serum alkaline phosphatase, as did normal subjects. We have also shown that the urinary excretion of riboflavin, N-methyl nicotinamide, creatinine, total sulphate, and inorganic and ethereal sulphate was, on the average, the same in the subjects with large livers as it was in the normals. At Igloolik, where the average nitrogen excretion per gram of creatinine was higher than at Southampton Island, the incidence of hepatomegaly was also higher, but the average nitrogen excretion in the hepatomegalics at Igloolik was less than it was in normal subjects. A difference was observed in the oral glucose tolerance of the two groups (Table XVI).

Horvath: Was it done once on each subject or more often?

Brown: Just once, and there were four subjects in each group.

Horvath: Were they adults?

Brown: Yes. We have data on only two subjects at the time their livers were large, as well as at the time when their livers were smaller; there is only one case in which the liver was of normal size. There was an increase in the glucose tolerance during that period of change.

Horvath: There is certainly a great deal of variation in glucose tolerance if done repeatedly on the same individual. Whether this is a significant difference or not, of course, I haven't given you a chance to say.

Brown: The difference is not statistically different.

Liver function tests have been done on large numbers of these people. Bromsulphalein tests on 29 subjects were normal, and, in fact, the bromsulphalein retention was very small. The ability to synthesize hippuric acid was also normal. We have data on basal metabolic rate in both

			Average
		[illegible]	7 42
		6	3 79
		36	0.97
		36	27 3
		57	522
		57	340
	9 9	57	9 4
	1 3	57	168
	[illegible]	57	46.9
	[illegible]	57	28.4
[illegible]	0.72	5	0.72
[illegible]	[illegible]	10	10.12
[illegible]	5 44	20	3.39
	[illegible]	44	15 4

TABLE XVI

Glucose Time Curves (Oral) in Normals and Hepatomegalics (Blood Glucose (Somogyi) mg/100ml.)

	Fasting	½ hour	1 hour	1½ hours	2 hours
Normals (4)	82	125	110	101	93
Hepatomegalics (4)	72	162	145	133	96

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groups and the average in the two groups was the same. We also determined blood volumes by a dye method, and again in the two groups the average plasma volume and total red cell volume were approximately the same. The counts of red and white blood cells, eosinophils, and the sedimentation rate, were the same in the two groups.

Ferrer: Have you any figures on the hematocrits in the two groups, i.e., representative of the race as a whole? Do these Eskimos run the usual hematocrit?

Brown: Their hematocrits and blood counts were a little low as may be seen in Table XVII. We have not found the polycythemia that has

TABLE XVII

Average Blood Counts in Southampton Island Eskimos

	Males	Females
Hemoglobin (gm. per 100 ml.)	13.3	12.7
Red blood cells (10^6 per cu. mm.)	4.7	4.5
Hematocrit (per cent)	40.15	39.72
White blood cells (per cu.mm.)	8,09	8,61
Eosinophiles (per cent)	8.72	10.31
Sedimentation rate (Wintrobe)	18.1	31.8

TABLE XV

Biochemical Findings in Normal and Hepatomegalic Eskimos

	Normals		Hepatomegalics	
	Number of Subjects	Average	Number of Subjects	Average
Total plasma protein (gm. per 100 ml.)	37	7 57	36	7 42
Plasma albumen (gm. per 100 ml.)	37	3 98	36	3 79
A/G ratio	37	1 20	36	0 97
Plasma N P.N (mg per 100 ml.)	37	27 5	36	27 3
Total plasma lipid (mg per 100 ml.)	61	520	57	522
Total fatty acids (mg per 100 ml.)	61	329	57	340
Lipid phosphorus (mg per 100 ml)	*61*	*9 9*	*57*	*9 4*
Total cholesterol (mg per 100 ml.)	61	173	57	168
Free cholesterol (mg per 100 ml.)	61	47 5	57	46 9
Free cholesterol X 100/total cholesterol	61	27 7	57	28 4
Lipid P/total cholesterol	61	0 72	57	0 72
Serum calcium (mg per 100 ml.)	14	9.93	10	10 12
Serum phosphorus (mg per 100 ml)	*14*	*3 44*	10	3 39
Serum alkaline phosphatase (K.A. units)	66	13 5	44	15 4

TABLE XVI

Glucose Time Curves (Oral) in Normals and Hepatomegalics
(Blood Glucose (Somogyi) mg/100ml.)

	Fasting	½ hour	1 hour	1½ hours	2 hours
Normals (4)	82	125	110	101	93
Hepatomegalics (4)	72	162	145	133	96

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groups and the average in the two groups was the same. We also determined blood volumes by a dye method, and again in the two groups the average plasma volume and total red cell volume were approximately the same. The counts of red and white blood cells, eosinophils, and the sedimentation rate, were the same in the two groups.

Ferrer Have you any figures on the hematocrits in the two groups, i.e., representative of the race as a whole? Do these Eskimos run the usual hematocrit?

Brown Their hematocrits and blood counts were a little low as may be seen in Table XVII. We have not found the polycythemia that has

TABLE XVII

Average Blood Counts in Southampton Island Eskimos

	Males	Females
Hemoglobin (gm. per 100 ml.)	13.5	12.7
Red blood cells (10^6 per cu. mm.)	4.7	4.5
Hematocrit (per cent)	40.15	39.72
White blood cells (per cu. mm.)	8,09	8,61
Eosinophiles (per cent)	8.72	10.31
Sedimentation rate (Wintrobe)	18.1	31.8

been reported by others (5) in the Eskimos, but as I said before, we have studied only two groups. All that can be said is that it did not occur in our group

Ferrer Where were the venous samples taken?

Brown The antecubital vein.

Burch Did you find sickle and target cells in the blood?

Brown No

Burch Are the sedimentation rates abnormally high there?

Brown The sedimentation rate in the Eskimo is very high as a rule, and there are several possible explanations for this The incidence of upper respiratory tract infection is very high. It is high whenever they are being visited, and it was high during our work. Two characteristic sounds of the Eskimo camp are the howling of the dogs, and the coughing and spitting of the natives Frequently they are practically all coughing and spitting There are therefore many infective reasons for this elevation of sedimentation rate We have no fibrinogen determinations on these people, but it will be remembered that the plasma globulins were normal.

Burch No leukocytosis?

Brown No but there was an eosinophilia which we have related to the parasitic infections which they showed.

Shumacker Was the rest of the differential normal?

Brown Yes, it was.

Crismon Did you compare plasma volumes with those of a control group?

Brown We did only a few on ourselves to establish the method in our hands. Prof Magnus I Gregersen s figures for normal subjects were used as a basis for comparison.

Crismon. They were not different?

Brown The plasma volumes were not higher in the hepatomegalics than in the normals.

Travell What type of parasites did you find?

Brown The one which created the greatest interest was *Trichinella spiralis* (16,17 18 19) We found eosinophilia, positive skin tests with *Trichinella* antigen, and positive precipitin tests The serological tests were done by Dr E Kuitunen-Ekbaum, School of Hygiene, University of Toronto. The organism itself was found in the polar bear

Talbott Is it the only animal that carries the *Trichinella*?

Brown Dr Kuitunen has found it in other animals

Shumacker Where do they obtain the iron in the diet? Is it only in the meat?

Brown. In the meat, organs and muscle.

Talbott Is walrus a red meat?

Brown. It is highly pigmented

Burch Were the dogs infested with roundworms?

Brown Yes, some of them

Burch Visceral larva migrans is found in a number of people who live in close association with dogs It is characterized by a marked eosinophilia Hepatomegaly is common in visceral larva migrans.

Brown Do they become ill with this condition?

Burch They can be clinically ill.

Brown We found no relation between hepatomegaly and physical fitness these people could have quite large livers and be perfectly well

Burch That is true of visceral larva migrans, but they also have visual disturbances

Brown Of what sort?

Burch Impairment of vision due to direct retinal involvement

Brown We saw no abnormal fundi except for change in the arterioles. They have errors of refraction, opacity of the cornea in the older people and also pterygia. In children there is sometimes a softening and ulceration of the cornea

Tarell Did these people have clinical symptoms of acute trichinosis? I am interested because of the disturbance of creatine-creatinine excretion which infestation with this parasite produces.

Brown Yes, they did.

Shumacker Were subjects who were ill with trichinosis included in your group?

Brown No We did not see fulminating case of trichinosis during the time we were there As a matter of fact, the one case I thought might be acute trichinosis turned out to be typhoid fever In 1948 there was a small epidemic of typhoid fever on Southampton Island.

Tarell Did you do any creatine determinations, and if so did you examine its output in the urine, or only the creatinine?

Brown Only the creatinine

Burch What about rheumatic fever?

Brown There was no evidence of rheumatic fever or rheumatoid arthritis There was a lot of degenerative joint disease This may be illustrated by the decrease in height which occurs with age. In Figure 11 average heights and weights of the Eskimos at various ages are shown, as compared with Quetelet's group It may be seen that the time at which loss of height begins is earlier in the Eskimo and it occurs particularly early in the female. One's general impression is that these people age very rapidly and the decrease in height can be used as one means of quantitative description (20)

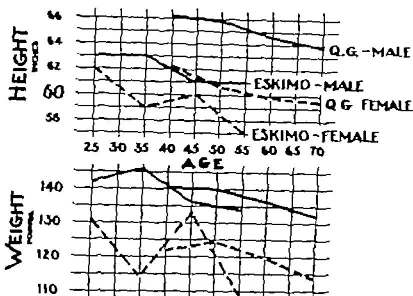


FIGURE 11 Decrease in height and weight of the Eskimos with advancing years as compared with a control group

Carlson What was the change in plasma volume and blood volume?

Brown. It was quite high. In Figure 12 are shown the average plasma volume, total red cell volume, and B.M.R., in the Eskimos during the summer months at Southampton Island

The plasma volume was determined with T 1824 (Evans blue) and Gregersen s values for averages in normal subjects were used for purposes of comparison. The plasma volume early in the summer was 42 per cent above normal. The red cell volume was increased to a lesser extent. All the determinations were made on men (9)

Behnke Do you know whether or not there is a marked increase of hemoglobin during the wintertime?

Brown. We have no hematocrit or hemoglobin measurements done during the winter We do know nitrogen excretion is the same, and that their plasma lipids are the same in winter as in summer but we have not repeated all the biochemical and hematological studies during the winter

Blair Are normal white levels used for comparison with the B.M.R. s. of the Eskimos in Figure 12?

Brown. DuBois standards and charts were used with the usually assumed respiratory quotient. The R.Q calculated from our dietary experiment was a little different, but it would make the results only 2

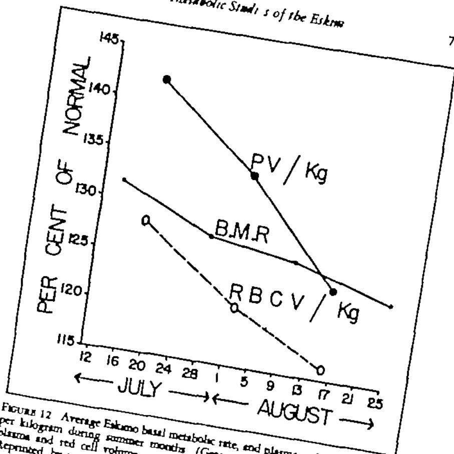


FIGURE 12 Average Eskimo basal metabolic rate, and plasma and red cell volume per kilogram during summer months (Gregersen. Average normal values for plasma and red cell volume per kilogram have been taken as 100 per cent.) Reprinted, by permission, from Brown, G M Bird, G S Boag, L M Delahaye, D J Green, J E Hatcher J D and Page J Blood volume and basal metabolic rate of Eskimos *Metabolism* 3, 247 (1954)

per cent too high All three levels, plasma volume total red cell volume and basal oxygen consumption, dec ease during the period of warm weather from the middle of July through the end of August.

Blair Do the B M R s represent a single determination, the average of a number or what?

Brown The points in the figure represent the averages of a number of determinations on a number of subjects

Seller How basal are the B M.R s Dr Brown?

Brown. That is a very good question First to be considered is the

state of mind of the subjects. Our subjects were so relaxed that one of the problems was to keep them awake. The apparatus was taken into their tents, and the determinations were made when they were still in their own sleeping bags

Blair Did you do any PBI determinations on these subjects?

Brown No but Gottschalk (21) has done that on a group at Churchill and on Eskimos at Chesterfield Inlet and Southampton Island. The average level of serum PBI was higher at Southampton Island than at any other place

Blair Were any such data obtained during the winter months?

Brown No it will be noted that this is the reverse of what is seen during short term cold exposure At that time there is, of course, constriction of plasma volume, and the total red cell mass also becomes smaller However Conley and Nickerson (22) found that at the end of six days of cold exposure there was a definite return to normal Our suggestion is that there is a phasic response. During the period of vasoconstriction due to cold, there is diminution of the blood volume and during the period of vasodilatation, with comparative enhancement of the peripheral circulation, there is an increase in the circulating plasma volume. At this stage as we have shown, acute cold exposure will cause greater vasoconstriction than in the nonacclimatized subject (23 24,25 26 27 28,29) and changes in the plasma volume are presumed to occur

Ferrer Have you done circulation times in those two periods?

Brown No we have not done that.

Behnke How do you explain the elevated basal metabolism?

Brown Exposure to cold.

Behnke Are the Eskimo subjects all fat?

Brown They are all reasonably well covered.

Horvath What is the temperature during June in contrast to that in July and August?

Brown During the first part of July it is pleasantly warm. The average minimum temperature in July and August is 38 F and the average maximum temperature 53 6° F

Horvath You would have to extrapolate the curve in Figure 12 so it would be still higher

Coffey You think it is high during the cold period?

Brown If we expose a subject to cold let us say for something like from six to ten days, the plasma volume first falls and then tends to return to normal That is what Conley and Nickerson (22) have described. If the cold is continued my suggestion is that the plasma volume will increase and reach a new plateau, the height of which is in relation

to the degree and duration of cold exposure. At this level we have found, and Carlson (30,31) also that in people who have been exposed for a long time, there is enhancement of the peripheral circulation, i.e. increased blood flow through forearm and hands and increased skin temperature of the forearm while at rest, but on acute cold exposure there is again vasoconstriction. We have not yet done the experiment, but I expect to find a reduction of blood volume during the acute cold exposure of the acclimatized person. Another conclusion which may be drawn from our data, is that the increased blood volume is a factor in maintaining visceral circulation at an adequate level despite the enhanced circulation through the extremities If there were no increase in blood volume, we should have to say there was a proportionate reduction in the circulation to the viscera.

Burch Would that be true of the heart rate change?

Brown There is no change in pulse rate

Burch How about stroke volume

Horvath That might change.

Burch. Are those variations outside the errors of the method for measuring blood volume?

Brown. Yes The increase in plasma volume is about 42 per cent, on the average.

Ferrer At what time did you take the blue dye sample on these subjects?

Brown. Specimens were taken at 10 20 and 30 minutes.

Burch You said the change was 15 per cent Is that significant?

Brown. Yes it is.

Crismon Is it presumed that during the exposure to cold, the heightened blood flow through the skin of hands and feet is accompanied by increased blood flow through the skin of the thorax and the rest of the trunk? Is all of the skin better perfused?

Brown Our own work has been on the hand and forearm only but in view of the skin temperature changes which have been recorded on other parts of the body one would say that there is increased blood flow through the face and some of the trunk. However I recognize the possible fallacy in drawing conclusions about blood flow from changes in skin temperature.

Pagé That would imply a greater heat loss when adapted to cold.

Brown. Yes.

Talbott That is associated with normal vasoconstriction or vasodilatation?

Brown That is while they are at rest.

Talbott If there is greater heat loss and blood flow there will be vasodilatation in the periphery

Brown Yes. High plasma volumes were obtained on a group who showed greater blood flow through the extremities. There is another relation which might be mentioned here, and that is the one between the B.M.R. and the blood volume In thyrotoxicosis, plasma and total red cell volumes are increased With elevation of B.M.R in patients with thyrotoxicosis of about this level (Figure 12) one finds just about the same elevation of plasma and red cell volume as has been found here (32,33)

Ferrer You have not done cardiac output measurements by blue dye?

Brown No, we have not.

Behnke What is the respiratory quotient?

Brown. Calculated from the observed dietary intake, it was 0 76.

Behnke Is part of the elevation of the basal metabolism due to the high protein in the diet?

Brown We do not know We have not done B.M.R.s after the protein intake was reduced However, in the experiment of McClellan, Spencer and Falk (34) it was found that two men put on a meat diet for a year showed no elevation of B.M.R except during the first month, when it was very slight An attempt was made with our data to relate B M.R. to nitrogen excretion, but it was impossible to arrive at any definite conclusion.

Behnke You calculated the respiratory quotient, but did not measure the carbon dioxide?

Brown That is right

Behnke Did you use the closed system with pure oxygen.

Brown A Benedict-Roth *apparatus* was used.

Ferrer Did you measure any plasma volumes on the medical personnel?

Brown Yes we found them within the normal range.

Pagé You said you found the same respiratory quotient at three different periods.

Brown No The respiratory quotient was calculated from the original dietary experiment (Tables V VI, and VII) We have no observations on respiratory quotient based on gas analyses.

ASCORBIC ACID METABOLISM

There are some interesting features to the metabolism of ascorbic acid in the Eskimo and it may well be that they are not unrelated to the problem of the hepatomegaly We have first *of all a series of whole* blood determinations made at Southampton Island in 1947 (Table

TABLF XVIII
Ascorble Acid Content of the Whole Blood of
78 Eskimos of Both Sexes and Various Ages

No of Individuals	Ascorbic Acid mg. per 100 ml.
3	0 0 0 19
13	0.20 0 39
19	0 40 0 59
22	0 60 0 79
13	0 80 0 99
7	1.00 1 19
1	1.20 1 39

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XVIII) As may be seen, the levels are low It should be remembered that the determinations were made during August and the first part of September a time when fresh meat is available and perhaps in greater quantity than it is at other times of the year It is also the time of the year when green things, such as berries, leaves, and roots, are available. The specimens were taken at odd times during the day and not during the fasting state. What is a normal level of whole blood ascorbic acid is a matter for discussion. If we belong to those who say it is 0.80 mg per 100 ml almost 75 per cent of our group were below normal levels If we consider it to be 0 60 mg per 100 ml., about 40 per cent were below normal levels This is not particularly surprising in view of their vitamin C intake. At Igloolik the ascorbic acid determinations were done by Dr Morley G Whillans, Superintendent Defence Medical Research Laboratory Toronto Ontario who was with us for one trip He worked over a period of three weeks and during that time there was a handsome catch of fresh seals He observed two completely different groups in that period and probably as a result there are two humps in the distribution of the data. The average fo the entire group was 0 80 mg per 100 ml but the peak of the first hump in the data was about 0 35 mg. per 100 milliliter This part of the curve concerns his earlier determinations.

TABLE XIX

Summary of Loading Experiment with Ascorbic Acid in Eskimos and in Controls

	Control Day			12th Day			14th Day		
	Whole Blood (mg per 100 ml.)	Plasma (mg per 100 ml)	Urine (4 hr mg.)	Whole Blood (mg. per 100 ml.)	Plasma (mg. per 100 ml)	Urine (24 hr mg.)	Whole Blood (mg per 100 ml.)	Plasma (mg. per 100 ml.)	Urine (24 hr mg.)
9 Normal Eskimos	0 55	0 54	36.6	0 91	1.29	275.8	0 92	1 15	270.8
10 Hepatomegalic Eskimos	0 61	0 78	90 6	0 96	1.29	298 3	1 09	1 32	399 1
9 Controls	1 12	1 18	15 4	1 49	1 78	196 0	1 42	1 60	180 1

Table XIX shows some of the results of an experiment in which 19 Eskimos were given 1,000 mg. of ascorbic acid on each of two days, in divided doses, and then 100 mg three times a day for 12 days. A control group of young people in Kingston was treated in exactly the same way. The first point to note is the low level of ascorbic acid in whole blood and plasma in the Eskimos. In the control group the figures were quite reasonable, with 1.12 mg per 100 ml. for whole blood and 1.18 mg per 100 ml for plasma, whereas in the Eskimos the levels were much lower We have in the Eskimos some determinations of ascorbic content of the white blood cells, and in the beginning the level was about 8 mg per 100 ml of white cells At the end of the experiment it had more than doubled.

The second point is that excretion of ascorbic acid in the urine was a good deal higher in both groups of Eskimos than it was in our control group In the control group it was only on the average 15.4 mg. per 24 hours whereas in one group of Eskimos it was 90 and in the other 36.6 mg. per 24 hours This was the situation before the loading doses of ascorbic acid, and after the loading we observed the same thing At the end of the experiment, the average blood and plasma levels were not as high in the Eskimos as in the control group but the urinary ascorbic acid at all stages was much higher than in the control group

The third point is that the urinary ascorbic acid was higher in Eskimos who had hepatomegaly than it was in those who had livers of normal size

Dugal Is the difference 0.77 and 0.54, in ascorbic acid significant?

Brown. No it is not There is no significant difference between the two groups of Eskimos with respect to the levels in whole blood and plasma The difference in the urinary excretion on the 14th day is significant at about the 5 per cent level

About four years ago there was an experiment conducted here at Fort Churchill by Dr LeBlanc, and Dr G Marier of the Defence Research Board, Defence Research Medical Laboratory Toronto Canada, in which a group of 15 soldiers were fed an ordinary army ration, and another group of 15 received 510 mg of ascorbic acid a day as a supplement There was a control period of 14 days here at Churchill during which they were not out very much, and then there was a period of exposure which involved outdoor exercise for 27 days Finally there was a short follow-up period These subjects, then, were loaded for fourteen days before their cold exposure with 500 mg a day which was more than our loading dose Their blood levels were higher than in our Eskimos but about the same as we observed in our control group

Personal communication, 950

Their urine excretion of ascorbic acid increased during the cold but at no time did it approach the levels seen in the Eskimo Their blood and plasma levels *remained pretty constant* during that period of cold exposure In another group of white men in the cold (35) a diminished whole blood ascorbic acid was found during the early part of an eleven-day bivouac, and there was an increased excretion in the urine. Dr. Carlson (36) in his experiment with a one hour exposure of varying severity from subject to subject, found no change in blood ascorbic acid. Dr LeBlanc has recently done another experiment involving both caloric deprivation and exposure to cold and will speak of that later in the conference

In summary the Eskimos show plasma and whole blood ascorbic levels which on the average are lower than are considered normal, and at the same time they excrete an amount in the urine which is greater than that excreted by control groups, both in a temperate environment and during a short term exposure to cold. There is also the suggestion of a difference in this respect between those Eskimos who are hepatomegalic and those who are not.

VITAMIN A AND HEPATOMEGALY

During the past ten years there have been occasional reports in the literature on human chronic hypervitaminosis A One aspect of this problem is hepatomegaly which disappears a few weeks after the vitamin A medication is discontinued In the published reports there is nothing which sets it apart from the condition we have observed in the Eskimo *There are grounds for believing that the intake of vitamin A by the* Eskimos is fairly high. The importance of the sea mammals in the diet is obvious and of our two groups, the one at Southampton and the one at Igloolik, the group which consumed more of the meat of these mammals was the one with the higher incidence of hepatomegaly Hoygaard (8) made an estimate of the vitamin A intake of the Eskimo and considered that on the average they ingested about 50 000 International Units (I U) per day This will naturally vary from group to group, and from place to place

It is possible to bring about hepatomegaly in the rat by feeding either walrus or seal meat and the *hepatomegaly* is less in the warm than it is in the cold where the food intake is greater (Table XX) The effect of cold on liver weight in animals on an ordinary laboratory diet has been noted before, and the effect of a high protein diet at ordinary temperatures has also been noted However the effect of a diet of lean seal or walrus meat *ad libitum* for 28 days, is considerably greater than the effect on liver size of lean beef and this is particularly the case in the cold.

TABLE XX

Effect of Walrus and Seal Meat on Liver Weight in Rats

Diet	Liver Weight Per cent of Final Body Weight Room Temperature 6 C	24 C
Control	5 15 per cent	4 75 per cent
Beef	6 15 per cent	4 59 per cent
Seal	9 30 per cent	6 96 per cent
Walrus	9.84 per cent	6 41 per cent

Pagé Was there much difference in body weights between these groups, at a given temperature

Brown Yes. We saw the loss of weight which was mentioned here earlier Our rats were smaller than the ones you have been using. They were from 90 to 100 gm. when the experiment was started. There was, in the beginning, a loss of weight and then food intake and weight increased. However the weight gain was less in walrus- and seal fed animals than it was in the beef fed animals.

Dugal The liver weights are expressed in per cent of final body weight?

Brown Yes. They a e also large if we relate them to initial body weight

Pagé They would be larger in absolute weights

Brown Yes.

Pagé On a percentage basis it is always higher on a smaller animal We have to take that into account

B   ww Dr Stevenson has epeated this experiment with somewhat larger animals, and has confirmed our results The livers he observed were not as large on a percentage basis, as ours, either with his control diet or the diet of walrus meat, but he has confirmed the presence of hepatomegaly on a diet of lean walrus meat in the cold

Shumacker Do the absolute liver weights follow the same trend?

Bi wn Yes, they do

Blair With all rabbits on a controlled diet, those living for seven weeks at −25 C show a 10 to 12 per cent increase in liver weight when compared with those living at room temperature.

Their urine excretion of ascorbic acid increased during the cold but at no time did it approach the levels seen in the Eskimo Their blood and plasma levels remained pretty constant during that period of cold exposure In another group of white men in the cold (35) a diminished whole blood ascorbic acid was found during the early part of an eleven-day bivouac, and there was an increased excretion in the urine. Dr Carlson (36) in his experiment with a one-hour exposure of varying severity from subject to subject, found no change in blood ascorbic acid Dr LeBlanc has recently done another experiment involving both caloric deprivation and exposure to cold and will speak of that later in the conference

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TABLE XX

Effect of Walrus and Seal Meat on Liver Weight in Rats

Diet	Liver Weight Per cent of Final Body Weight Room Temperature 6 C	24 C
Control	5.15 per cent	4.75 per cent
Beef	6.15 per cent	4.59 per cent
Seal	9.30 per cent	6.96 per cent
Walrus	9.84 per cent	6.41 per cent

Pagé Was there much difference in body weights between these groups, at a given temperature?

Brown Yes We saw the loss of weight which was mentioned here earlier Our rats were smaller than the ones you have been using They were from 90 to 100 gm. when the experiment was started There was, in the beginning, a loss of weight and then food intake and weight increased. However the weight gain was less in walrus- and seal fed animals than it was in the beef fed animals.

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Pagé They would be larger in absolute weights

Br wn Yes

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Shumack Do the absolute liver weights follow the same trend?

Brown. Yes, they do

Blair With all abbits on a controlled diet, those living for seven weeks at −25 C show a 10 to 12 per cent increase in liver weight when compared with those li ing at room temperature.

Brown We can say then, that on a diet of lean walrus meat, and particularly in the cold hepatomegaly may be produced in the rat. Despite the considerable amount of work that has been done on hypervitaminosis A in animals, we could find nothing on liver size. Rodahl (37) comments on the hypertrophy of the adrenals, but we have not found any statement concerning the size of the liver Dr. J S McAuley in our laboratory at Queen s University has now done an experiment to determine the effect of increasing amounts of vitamin A on the liver size of the rat in the cold (Table XXI) The same control diet was used as

TABLE XXI

Vitamin A Intake and Liver Weight of Rats Kept at 60 C. for Four Weeks

Dietary Fortification Vitamin A (I.U./gm. rat weight per day)	Food Intake (gm per rat per day)	Liver Weight (gm. per cent final body weight)
Control Diet	15 9	4 76 per cent
+ 10	17 5	4.82 per cent
+ 25	15 0	4 76 per cent
+ 50	14.5	4 78 per cent
+ 100	15 0	5 12 per cent
+ 250	13 5	5 79 per cent
+ 00	10 1	6.44 per cent

in the other experiment, and it was supplemented by 10 to 500 I U of vitamin A per gram of rat body weight per day The supplement was given each day by a stomach tube. As can be seen in the table, there is an increase in liver size with increasing doses of vitamin A With toxic doses of vitamin A the food intake of the animals fell off and we intend to explore further the range between 10 and 50 I U per gram rat body weight per day

Dugal Do you think that hypervitaminosis A could not act indirectly by hypersecretion of ACTH? I read recently that a tremendous increase in liver weight could be produced in guinea pigs and rabbits with injections of ACTH (38)

Brown Yes But would not injections of ACTH produce histological change in the liver when they are so large.

Dugal In the paper that I referred to the increase in liver weight is attributed to an increase in glycogen and water content in the initial stages, and later to an increase in protein also There is no mention of histological changes.

Brown I am under the impression that it has been described. As for glycogen, the livers of the rats of the earlier experiments were normal What is the change in the glycogen in your animals?

Dugal I do not remember

Brown You said there is an increase in glycogen and water content. In hypervitaminosis A there is a diminution of liver glycogen. Dr Stevenson did liver glycogen determinations in his experiment and found that it was about 50 per cent of the average normal in the walrus-fed rats in the cold.

Burch Was the unit per whole liver or per gram of liver?

Stevenson Per gram.

Burch Therefore, the weight of liver because of total water content, might remain unchanged

Stevenson We did not observe quite as much hypertrophy The average absolute weight of livers on the control diet was 11 gm and on the walrus meat diet, 13 gm. the controls had 3 16 per cent glycogen, and the walrus-fed animals 1 6. I do not think the water would account for that difference.

Pagé Were those findings in fasted animals?

Stevenson No

Pagé You might obtain the reverse picture if you fasted them. At room temperature, rats on a high fat diet have higher fasting liver glycogen, and lower nonfasting values, than rats on a low fat diet This was reported by Samuels Reinecke and Ball (39) We found that on a low fat diet the fasting liver glycogen is higher in cold-adapted rats although the reverse is true in the nonfasting state

Shumacker Were the changes in liver weight, as compared with body weight, significant with high doses of vitamin A when there was a low dietary intake?

Brown Yes.

Shumacker Was this change significantly greater than with a similar degree of starvation?

Brown That is what we have not yet done. Another suggestive piece of evidence that we have consists of plasma vitamin A determinations This year when Dr McAuley began work on the vitamin A hypothesis, he brought out some specimens of plasma obtained in 1949 They had

been stored in the frozen state in the dark for four and-one-half years. The average level of vitamin A, as determined in those subjects with normal livers, was only 50 per cent of what it was in those whose livers had been enlarged at the time these plasma specimens were collected.*

In summary the following points suggest that a high intake of vitamin A may have something to do with the hepatomegaly seen in Eskimos: (*a*) the incidence of hepatomegaly was *higher in the group who ate* more walrus and seal meat (*b*) hepatomegaly may be produced in rats by feeding walrus and seal meat (*c*) *hypervitaminosis A is characterized* by hepatomegaly in man and in the rat (*d*) the Eskimo's natural diet (seal and *walrus meat*) *has a high vitamin A content* (*e*) *in a* group of stored specimens of Eskimo blood plasma, twice as much vitamin A *was found in those samples which had come from* subjects with hepatomegaly as in the ones which had come from normal subjects†

I shall suggest to you now that there may be a relation, not only between the high intake of vitamin A and the hepatomegaly but also between *the high intake* of vitamin A and the metabolism of ascorbic acid. There are a number of suggestions of interaction between ascorbic acid and vitamin A The symptoms, signs, and pathological findings, of hypervitaminosis A have points in common with those seen in scurvy There are also similarities between the signs of scurvy and those of vitamin A deficiency It has been shown that the scorbutic guinea pig is more vulnerable to vitamin A toxicity than is an animal receiving a normal amount of vitamin C.

If large doses of vitamin C are given to guinea pigs and rats, they are provided with protection against small and moderate doses of vitamin A, but not against very large doses (37) of vitamin A. *Administration* of large doses of vitamin A to animals is followed by a fall in blood ascorbic acid Vitamin A-*deficient rats, exhibiting some of the signs of* scurvy may have these signs relieved by massive doses of vitamin C (40) In cattle, *the ability to synthesize ascorbic acid has been shown* to be impaired in conditions in which there is vitamin-A deficiency (41) In the Eskimos we studied there was vitamin C deficiency with *low blood* levels and low tissue content of ascorbic acid, as shown by the white cell studies that were done, but they seem to get *along reasonably well* in the cold Is it possible that they manage to do so in part because of their high vitamin A intake?

Horvath Isn't it somewhat peculiar that other Eskimo groups do not

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*These determinations were made in the laboratory of Dr L. Bradley Pett, Chief, Nutrition Division, Department of National Health and Welfare, Ottawa, Canada.

†Determinations on sera obtained in the summer of 1954 have shown higher serum vitamin A concentration in those Eskimos who have clinical hepatomegaly than in those those who have livers which cannot be palpated.

have the hepatic involvement you found in these particular subjects? They certainly eat the same foodstuffs including the walrus and seal which also have high vitamin A contents. Do you think there may be a difference between the Eskimo groups in these islands, in their ability to absorb and utilize vitamin A?

Brown. I am a little skeptical of some of the reports from other groups. All clinicians are aware of discussions about liver size.

Allen. There is, perhaps, an even more pertinent question. Why do such a small percentage of the subjects have a high vitamin-A intake and why do such a small percentage have enlarged livers?

Horvath. Yes, that is even more important. Dr Brown, on a diet of the same general type, apparently many of the subjects had a disappearance of the three fingerbreadths an hepatic decrease below the right costal margin. Is that right?

Brown. I did not go into that, but the diet was not of the same general type. We did a number of dietary experiments which I need not go into in detail. What they actually amounted to was the substitution of casein, lactose, and sucrose, for natural foods. I think in those dietary experiments we were lowering their vitamin-A intake.

Horvath. How long were they on these diets?

Brown. Four weeks. In hypervitaminosis A the hepatomegaly disappeared in from ten days to two weeks, in the clinical cases reported. Why all the Eskimos do not show it is another question, but I would point to the variations found in plasma vitamin A concentration and to the fact that there has to be quite an increase in liver size before there is a palpable enlargement.

Shumacker. Disregarding the question of hepatic enlargement, does the high vitamin A intake help the Eskimo adapt in the cold?

Carlson. There is the possibility that vitamin A has a sparing action (37). As the amount is increased, it blocks or impairs the vitamin C.

Brown. That corresponds with the information available.

Carlson. If the vitamin A intake were sufficiently high, considerably less vitamin C would be required. I believe that there is also a utilization in the adrenal, and that vitamin C is shunted to vital areas during this time.

Horvath. When we look at those values we find very low vitamin C levels in the plasma and extraordinarily high excretory levels in the urine, in contrast to those observed in normal people. Does that mean a specific abnormality in the kidney which throws out the vitamin C when there is an excess of A available?

Brown. I do not yet know the answer to that.

Horvath I do not see how it fits into this pattern of a preserving or assisting factor

Behnke What is the differential diagnosis of enlarged liver in the Eskimo and what might cause this finding? How about a cystic condition?

Allen. I do not know whether there are any cystic diseases of the liver in the Eskimo In the white population they are so rare that their importance is minimal. I think the data which Dr Brown has shown would *indicate that this condition is* physiological therefore he was *able to reverse it*. We do not have to go any farther than that.

Talbott The fact that liver biopsies were done strengthens that concept.

Behnke Parasitic diseases cause enlargement of the liver They would not necessarily *incapacitate an individual, would they?*

Horvath I think this does not incapacitate at all. These subjects had parasitic diseases

Shumacker Hydatid disease of the liver could occur without increase in size. There could also be asymptomatic enlargement of the liver with parasitic disease

Horvath What about Dr Allen's question as to why there is such a small percentage of this abnormality?

Blair Is it a small percentage? After all, one third of the population is a rather large proportion, especially among young individuals.

Burch How do you know that all of them did not have large livers?

Allen Dr Horvath and I are concerned *that* presumably *a third of* these people have enlarged livers that is a little bit hard for me to understand.

Horvath Especially if it is a physiological process They are all exposed to the same stress stimuli of excess of vitamin A.

Brown Not quite There is perhaps an answer in the incidence of hepatomegaly in different age and sex groups It is less frequent in females particularly young females, and they are the ones who are probably going to have more bannock, and so on, and less walrus meat and blubber *I have the idea that that may explain the age and sex* distribution.

Horvath. That diet is also available to their husbands or other members of the family It would therefore reduce the error of incidence

Brown. There is a difference in the eating habits of adolescent girls and adult men. There is the same suggestion in the higher incidence of hepatomegaly at Igloolik, where the intake of meat was higher than at Southampton Island. The figures suggest that *it is not the protein in*

the meat which produces the condition, but some other factor That is to say the figures are consistent with the hypothesis that it is due to an increased intake of vitamin A

Birch Did you check the literature to see what the incidence of large livers is among arthritic patients who have been treated with large quantities of vitamins A and C?

Brown So far as we know there is no good information on that but from the reports that have been published it can be said that there is a variation in the tolerance of individuals to vitamin A Some persons have difficulty with much smaller doses than others That is not surprising

Birch That was my point concerning you subjects individual variations surely must ha e existed Fifty thousand units is high, but not extremely so.

Brown That is just Heygaard s estimate, but it is the best one available.

T asell There is the additional factor of cold in the Eskimo

Dugal In your rat experiments did you observe any enlargement f the liver with vitamin A, at room temperature

Brown There is an experiment now being c nducted by Dr J S McAuley which will permit factorial analysis with tw temperatures, two levels of protein (casein in each case) two levels of fat nt ke and two levels of vitamin A intake We shall then ha the nswer t your question.

Carlson The data from the beef se l and w lrus int kes sh wed a difference. Was that due to the volume f f od t ken k you think

Brown It may be but as Dr Stevenson sa l with al k deprivatn there is a comparative enlargement of liver

Stevenson In the cold?

Brown Yes The beef fed animal t k more than did the walrus-fed animals, so that would not explain the difference Vitamin A content of beef varies very much from sampl t sampl s far s we can find out, but in no estimations that we have me a ons have the results been as high as are found in walrus meat

Dugal Was there n enlargement f the adrenals when the liver increased in size?

Brown Yes. In the w lrus-fed animals the drenals were larger

Cr mow. The role of ascorbic acid in the enzyme pattern has not been determined. How ever it seems to be essential in the destruction of homogentisic acid to fumar te and acetoacetate

I was wondering whether animals that had devel ped scurvy on ithout vitamin C, even though well supplemented with itamin

showed any signs of the vitamin A replacing the vitamin C in homogentisic acid metabolism.

Brown As far as I know that has not been done.

Crism n One possible function of ascorbic acid is its role as a reducing agent for the conversion of iron from the ferric to the ferrous form

Travell Dr Brown, do you believe that the increase in liver size is due to increased fluid content?

Brown I think that is a definite possibility Dr Travell.

Ferrer Did you, by any chance, make measurements of plasma volumes in those who had an enlarged liver and then again at the time when the liver was observed, by palpation, to have decreased?

Brown. No We have no before and after plasma volumes.

SOME VASCULAR CHARACTERISTICS OF THE ESKIMOS

Burch Dr Brown, is there anything unusual about the blood pressure of the Eskimo?

Brown Yes, there is Some of them, by the way are hypertensive, and some are arteriosclerotic Table XXII shows some data on the blood pressure response to cold. In these experiments, the hand and forearm were in a cold water bath for one or two hours during the course of the plethysmographic studies of hand and forearm blood flow The pressures in the control subjects were a little high to begin with. How much of that was due to apprehension, I do not know There was a good deal of nervousness displayed by some of the subjects but others appeared not to be too concerned about the experiment As can be seen from the table, the pressor response is much greater in the Eskimo.

Blair What was the difference in symptomatic response and subjective reaction to immersion between the Eskimo and the control?

Brown. In 5 C. water baths, for instance the Eskimos complained of severe coldness and of a deep aching sensation for a few minutes, but actually two out of three went to sleep during the experiment. The white men complained of pain as well as a sensation of burning in the 10 C. water bath, and there was so much pain and burning discomfort in the 5 C. water bath that the experiment had to be terminated at the end of 60 minutes (29)

Allen. You mentioned hypertension. Can you tell us how many subjects there were, what the blood pressure was, the age distribution, and roughly the value?

Brown I cannot give you all that, but I can make a few observations. At Igloolik Island for instance, where we examined 100 people four were hypertensive At Southampton Island, in a morbidity survey carried

TABLE XXII

Effect on Blood Pressure of Immersion of Hand and Forearm in Cold Water

	Water Temp. C		Before Immersion	On Immersion	Average During Immersion	Change in mm Hg	Number of Subjects
ESKIMOS	3 5	Systolic	101	120	142	+ 41	3
		Diastolic	64	89	97	+ 33	
	10	Systolic	101	105	114	+ 13	3
		Diastolic	63	75	80	+ 17	
CONTROLS	5	Systolic	123	134	129	+ 6	5
		Diastolic	91	105	101	+ 10	
	10	Systolic	123	120	120	− 3	5
		Diastolic	89	91	91	+ 2	

out in the same way three out of 182 subjects were found to be hypertensive We also have electrocardiographic evidence of coronary heart disease in four of that number

Allen What was the degree of hypertension?

Brown Well above the 150/100 level.

Allen If one believes with Keys (42) that a high fat diet of primary importance in the genesis of atheromatosis presumably the Eskimo would have a high incidence of this condition. Keys has indicated that those subjects who eat about 42 per cent of their calories in fat have a relatively high rate of atheromatosis, and I believe you said that with great variations your subjects averaged about 68 per cent of their total calories in fat Do you have any data on that?

Brown All I can say is that it exists The age distribution of the Eskimo population is very different from ours They age very rapidly there are a number of accidental deaths, and treatment facilities are not as accessible to them as they are to us Thus difference in age distribution must be born in mind. We frequently saw changes in temporal and brachial arteries, and we have as I have said, electrocardiographic evidence of coronary atherosclerosis and pathological evidence in the case of our one postmortem examination. These points are not an adequate answer to your question. To my knowledge there are no significant figures on the incidence of atherosclerosis in the Eskimo

Allen I think you said that you had reviewed the histories for acute rheumatic fever Do you know whether acute myocardial infarction, or any congestive heart failure might contribute to coronary heart disease?

Brown We have not seen acute myocardial infarctions, but we have seen angina of effort

Blair What may be of greater significance than gross changes in blood pressure during the cold pressor test is the response of your controls on immersion You received the highest systolic and diastolic response in the controls immediately upon immersion, and then it decreased during the period of immersion. This is quite similar to what we observed in cold pressor tests on a group of frostbite patients. Their response was quite different from the Eskimos, whose blood pressure built up gradually during the period of immersion. Were the Eskimos and the controls immersed for the same length of time?

Brown No the Eskimos remained two hours in each of the baths the controls were in the 5 C. bath for an hour and in the 10 C. bath for two hours.

Blair At what intervals were blood pressures taken?

Brown About every five minutes.

Blair In most of the Eskimos did you see this steady build-up of pressure all through the period of immersion?

Brown Yes. These are averages of all the pressures during the period of immersion.

Blair The Eskimos pressure kept building up all during immersion, but the controls, who were not Eskimos, responded with an initial maximum which fell off during the period of immersion. Is that correct?

Brown Yes, but the initial change was not as great as that seen over the entire period in the Eskimos

Blair In white subjects we have never observed anything except the initial maximum response, and the gradual decrease during continued immersion. This is an interesting difference in response between the Eskimo and the white man.

Brown The blood flow of the Eskimo in these water baths is always higher in the hand and forearm than in the white man, but the degree of constriction is not greater in the white man than it is in the Eskimo in terms of reduction of blood flow per 100 ml of tissue

Barton You say the white men put their hands in water at 5 C. for one hour? That is a very drastic pressor test indeed is it not?

Brown Yes.

Barton Two minutes is enough for most patients

Brown These were medical students Actually we had to cut it short at sixty minutes.

Barton That is quite different from the cold pressor test on which there is a lot of data.

Brown The figures at the time of immersion are somewhat comparable, but not the rest.

Barton Is that a calculated mean pressure change

Brown Yes.

Shumacker The fact that some of the Eskimos actually went to sleep during the test is interesting because they still had a very marked pressor reaction. There was no difference in the pressor response whether they went to sleep or stayed awake?

Brown Not so far as I know

Blair Many investigators suggest that the elevation of pressure obtained in cold pressor studies on frostbite patients is primarily due to severe pain upon cold immersion

Horvath Perhaps there was a different impression of pain between these two groups.

Brown Their tolerance of pain is much greater than ours, but that is not, of course, the same thing as a pain threshold. However because we were interested in the subjective sensations, they were asked from

time to time, during these experiments, what pain or discomfort they were having Aside from discomfort, they reported pain for a shorter period of time than did the controls.

Horvath Do the Eskimos spend a good deal of time working on a catch in the water?

Brown They often work with their hands in sea water which is as cold as these water baths

Carlson Pecora (43) reported a change in the cold pressor test results, comparing individuals at the end of winter in San Antonio, Texas, and Fairbanks, Alaska.

Stevenson Were the tests on the Queen's University students done in the summer or winter?

Brown In October and November

Burch How accurately does the Eskimo know his age? What criteria did you employ in arriving at the conclusion that they were aging more rapidly?

Brown The ages of those who were adolescents and a little older could be determined fairly accurately but beyond that it was more difficult We obviously had to rely on the information we were given. We were extremely fortunate in having the interpreter we did, because he had considerable knowledge of the district He would, in some cases, relate age in terms of events that the subjects remembered, and the data of which he knew

Burch What were criteria for rapid aging?

Brown The only one quantitated was the decrease in height.

Talbott That was based on osteoporosis of the spinal column?

Brown. It is probably a degenerative affair

Talbott Do we know from any other studies whether osteoporosis occurs at an earlier age in the Eskimo than in the control subject?

Brown There is no other information.

Burton. Is it the decrease in height as the Eskimo grows older or is it the height of the population?

Brown. It is the height of the population.

Burton. It is conceivable, is it not, that short people might survive longer? It may be that you are putting the wrong interpretation on it.

Brown As you say it is possible, but I think the other explanation is also a likely one

Horvath Perhaps the younger people are getting better food, and more food, than the older ones

Brown Yes. I think that is more of a possibility

Shumacker What do the blood vessels in the fundi of these adult Eskimos look like compared with people in your own province?

Brown There is some retinal arteriosclerosis, but we found no very abnormal fundi. We examined all of the adults for this.

Allen. How about the incidence of diabetes?

Brown We did not see it. Would you expect it, Dr Allen? The diabetics might have died out over a long period of isolation.

Allen. Yes, of course You are thinking about the elimination of family groups, but I had heard it stated, even in these conferences, that incidence of diabetes is very high in the Eskimo

Brown. All I can say is that we have not come across it.

Stevenson Would not it be their impaired sugar tolerance curve?

Horvath They have remarkable sugar tolerance curves

Bebake In the Eskimo and the control subjects, did you make any temperature measurements of the skin of the hand d ring, or following, immersion in cold water?

Brown. Yes. The observations in Table XXIII were made in a room at 20 C. That temperature was chosen because during July and August, when the experiments were done, it was found that that was the average temperature of the dwellings in which they were living they were comfortable at 20 C. with woolen shirt, woolen trousers, and mukluks The forearm skin temperature was higher in the Eskimos Subcutaneous temperature and muscle temperatures were not different. The rectal temperatures were not significantly different Forearm and hand blood flow were greater in these circumstances, that is at rest in a room at 20 C. The average hand temperature was not significantly elevated

Bebake Several years ago Prof C. P Yaglou, of the Harvard School of Public Health,* made some measurements on the return to normal of the temperature of the skin on the hand after the hand had been immersed in ice water, and he obtained some interesting curves I was wondering whether or not, in the case of the Eskimo the temperature returned to normal very rapidly compared with the temperature of the control subjects, in the ice immersion test

Brown We have done many immersion studies, but so far have not followed them from the cold temperature back to the warm

Bebake I believe there was considerable loss of weight in the Eskimos, as they grew older

Brown Yes.

Bebake It is of interest that in the average population that takes food *ad libitum* there will be a gain in weight of about ten per cent from ages 25 to 55 but in populations that have scanty food, for example, in some of the heavily populated South Sea Islands, there is a loss rather than a gain in weight.

* Unpublished data

TABLE XXIII

Blood Flow and Tissue Temperatures at Room Temperature 20 C.

	Group	No. of Subjects	Mean	S E.M	P
Forearm Baring Temperatures ° C.					
Skin	Control	33	30 5	±0.25	
	Eskimo	61	31.2	±0 17	0.02
Subcutaneous	Control	33	32 7	±0.23	
	Eskimo	67	32.9	±0 18	0 49
Muscle	Control	30	34 4	±0 19	
	Eskimo	65	34.6	±0 16	0 41
Hand Temperature C.	Control	5	32 6	±0.89	
	Eskimo	6	33.8	±0 47	0.21
Rectal Temperature C.	Control	31	37 3	±0 07	
	Eskimo	30	37 1	±0 06	0 14
Forearm Blood Flow cc/100cc tissue/minute					
	Control	4	3 0	±0 08	
	Eskimo	6	5.2	±0 11	0 01
Hand Blood Flow cc/100cc tissue/minute					
	Control	5	4.7	±0 19	0 01
	Eskimo	6	8 6	±0 43	

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Brown That is very interesting and may be applicable here.

Allen In your collateral reading, which must have been very extensive on this experience with the Eskimos, have you found any references to the incidence of atherosclerosis in the Eskimo? Has there been adequate necropsy material to give us any information?

Brown No there is very little postmortem material there have been few morbidity surveys of much account.

Sellers Very recently we had occasion to do fat stains on the coronary

vessels, aortas, and other tissues of rats which had lived in the cold room at 1 or 2 C. for more than a year and during which time had been receiving the usual laboratory ration.

In a high proportion of such animals, we found that in the intima and media of the coronaries and in the aorta there were definite deposits of stainable fat. However I am not satisfied with our control data At the moment, the rats of our colony that are of equivalent age do not show similar changes. I did not have a control group run concurrently at room temperature to compare with the animals that were in the cold

I should be interested to hear from anyone whether or not stainable fat is common in the vessels of rats, and what is thought of the continuous imposition of stress on the production of vascular disease

Barton There is the work of Constantinides (44) who stated that in the rat there is very little atherosclerosis At least it cannot be produced by feeding lipids, unless something is done about the large amounts of endogenous heparin (45) which are present I think it would be unusual to see lipid infiltration in the vessels of rats

Sellers Drs Hartroft, Ridout, Best, and I (46) have produced atherosclerosis in rats by feeding diets low in choline However our experiments were prolonged. In the last year or so Dr George W Igram, in Dr. Hartroft's section of the Banting and Best Department of Medical Research, University of Toronto has produced atherosclerosis, or deposits of lipids at any rate in the coronary vessels of rats within a month or so.

Barton. Lipemia may be easily produced, according to Constantinides (44) and others (45 47 48) if at the same time as lipid feeding we give protamine (47) the antagonist of heparin, or perform a thyroidectomy (49)

Talbott Did you take urine outputs? What is the fluid exchange in the Eskimo?

Brown. The urine volumes are high. It is not unusual to have a 24-hour urine volume of over 3 000 milliliters.

Talbott Was drinking water during this study period more available than at other times of the year?

Brown. No, not than at other times in the summer In the winter they have to melt snow and ice. They are great tea drinkers and take it as often as possible not a small cup but a large enamel one. Furthermore the interpreter told me that all Eskimos have nocturia.

Ferrer You mentioned doing some radiographic studies to determine the level of the right diaphragm. In the course of that study did you come upon any evidence suggesting that the middle or older age groups of Eskimos suffer from pulmonary emphysema? You mentioned the

constant cough, expectoration, and respiratory infection. I wondered whether you had any radiographic evidence of this disease.

Brown The radiographic evidence of pulmonary emphysema was not very striking Considering the unreliabilty of radiographic evidence, we could not, on that basis, make out a case for emphysema in the Eskimo

Blair Does not the coughing continue for only a short period of time, when the investigator or outsiders are there?

Brown. With some of them it is a year round affair a chronic cough with a mucopurulent sputum. When we did the glucose tolerance tests, for instance, we of course wished the subjects to be lying down while it was going on When we told them this they looked around and found tin cans to take to the cots with them as sputum cups. There was a spell of coughing after they lay down, and again when they got up.

Allen Do the Eskimos smoke?

Brown. Yes, as much tobacco as they can obtain.

Allen. Is that much?

Brown Yes a good deal

Stevenson Pipe?

Brown Yes, and cigarettes.

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A COMPARATIVE STUDY OF YOUNG ESKIMO AND INDIAN MALES WITH ACCLIMATIZED WHITE MALES

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WE ARE MAKING a study which is really not yet completed, of a group of Eskimo and Indian young men in the Northwest Territories around Aklavik (see map frontispiece)

This is a very unusual group of subjects and a word is necessary to explain their special status. The country whence they came is quite different from the district of which Dr Brown has spoken, because of the recent migrations. During the last 20 to 25 years a great deal of money has been made in the fur-trading industry This has led many of the Eskimo and Indian families away from the reservations and from their own Eskimo groups, and they have formed a pseudoculture which is based mainly on fur trading in the area surrounding Aklavik.

The Anglican missions have been in the district for a number of years, and have helped solve one of the problems confronting the parents, namely that of dealing with the children during the years when they are of school age Since school interferes with the family trapping and hunting which is going on, it has been the custom of both the Anglican and Catholic schools, to take in the young Eskimo and Indian children, and retain them on a sort of year round boarding school basis over the period from, perhaps six to ten years of age.

As a result these young men receive a completely different type of diet than they would normally ingest were they living under more primitive conditions, and they soon acquire habits and customs which can only be called Aklavikan and are not typical of the culture from which they originally came.

This Aklavikan group came to us in Fort Churchill a year ago, as members of the Canadian Army

We observed them in the field on several military exercises, when we lived and worked with them for several weeks at a time. We were also able to conduct some studies in the laboratory including both metabolic and cold-room work.

The thing we found most interesting in both the Eskimo and Indian

groups was the fact that they were far superior in their ability to cope with the cold than any of the acclimatized white troops with which we were working They not only showed the ability to tolerate longer cold exposure than the white personnel, but they seemed to show absolutely no incidence of cold injury despite the longer periods of exposure to very low temperatures. It was difficult at the time to decide just what was the reason for this and so we investigated their performance both in the field and in the laboratory quite carefully

Of the ten subjects, four were Loucheaux, both parents being pure Loucheaux. Three were Eskimo their grandparents had come originally from Greenland, but they were third generation Aklavik. Of the three others, one was a Slavey whose parents were both of this breed another was the son of a Loucheaux mother and a Scotch father and interestingly was named MacLeod. The third was the son of a Loucheaux mother and a Loucheaux Scotch father This group was extremely cooperative and, as I pointed out, had been educated in the church schools We found them very valuable subjects, and easy to work with.

A series of B.M.R. measurements, which I am sure will be of interest to you in light of what Dr Brown has said, was conducted during the month of August. We used the Sandborn metabolator and the standard tables for the normal white population were used in computing the B.M.R. s. The group had had some previous experience with energy metabolism measurements and were quite used to reclining with a mask on.

The usual clinical precautions were taken and of course, they were fasting As a group we found that the B.M.R. was only 2 per cent higher than normal The Eskimo group showed only a 5 per cent higher rate The pure Indian group was also plus 5 per cent, and the two breeds were minus 2 per cent.

These figures are means of a series which were taken over the month and represent from three to five B.M.R. determinations per subject. One familiarization measurement was also done which is not included in the data.

As I suggested, we found that the habits of these people were certainly not typical of the Eskimo-Indian culture, and they were quite used to the Army type of diet which they were receiving In the earlier days in camp they had begun to eat more sweets than they were used to but finally became very tired of sweet foods and during the period when the B.M.R s were taken, they were no longer eating such things as steamed fruit cake which we have in the ration packs, and chocolate nut bread. Furthermore they seemed to avoid taking any sugar in their beverages.

Observing these people in the field we found them far superior to the white personnel in terms of cold responses. They could certainly endure cold exposure much longer and there was no indication that they suffered from injury in the cold.

I should like to describe a few tests used to measure performance in the cold These were recorded in motion pictures and were done at temperatures of −38 to −40 F., with wind speeds of 35 to 40 miles per hour This transcribed in terms of wind chill is somewhere in the vicinity of 2,400

The first subject was a pure-blooded Loucheaux Indian and he worked at a job which consisted of moving a set of bolts from one side of a board to another with bare hands. It was a very pointless task, but we found it a good way to measure cold performance. He used two sizes of wrenches, a screwdriver and bolts which were in three sizes. The bolts and tools had all been permitted to reach ambient temperature, having been out at least two hours before the experiment started.

Blair Did you observe any evidence of metal burn, or similar cold injury?

Coffey No The subject gripped the wrench quite firmly and there was no suggestion of juggling it. This test continued for 6¼ minutes, during which time he paused twice to rewarm his hands by blowing on them.

Birch How long was he out in the cold before you started the test?

Coffey I think he came out of the tent when the experiment was about ready to begin and probably waited just a couple of minutes while the camera was set up

In another test, two Indians and an Eskimo loaded magazines barehanded This required picking up a cartridge and forcing it into a metal box. The metal was at ambient temperature and had been out of the tent for at least two hours. A third test was made with the man using anticontact gloves, which help in reducing the cold exposure

Birch In the test made barehanded, would the man have stopped spontaneously before he developed difficulties?

Coffey Yes, they were all instructed to stop immediately if they felt any severe pain, or believed they were likely to injure themselves. These tests of performance were made quite informally and the aura of an experiment was nowhere present

Stevenson Did you say they offered their services?

Coffey They volunteered after a discussion of the problem.

The next experiment was with a Loucheaux Indian. This time the exposure to cold during magazine loading was something less than a minute, i.e. not nearly as long as in the first case, where bolts were

moved from one side of a board to the other We carefully examined the subjects immediately after each experiment and during the subsequent days we were in the field we checked their hands carefully There was never any evidence of cold injury and certainly none of the common frostburn and skin peeling which one would normally expect.

Shumacker Would a dexterous Eskimo who lived in this neighbor hood, and who had not had any contact with the missions, do it as well?

Coffey I am not sure, but I have a feeling that he could certainly compete

Shumacker In other words, the fact that they grew up in the mission schools had little to do with the matter

Coffey The main influence of the Anglican and Catholic missions would be on their dietary habits and perhaps their philosophical approach, certainly not on manual dexterity In considering the performance, it was rather difficult to decide whether the individual differences were actually physiological or whether there were tricks of the trade and they were using a cold skill of sorts which enabled them to do more work and handle cold things simply by juggling, by using the more vascular parts of the hand, and perhaps by more careful organization of work.

We noted that they displayed a tendency to plan their work so that they did not expose their hands more than was necessary We saw also that they used a method of rewarming in which the body usually the abdomen or the genitals, was used to warm up the hands when they did become cold.

In questioning them, we were not able to find out much from the men themselves All their lives they had been used to working in the cold They had earned their living by dropping muskrat traps in icy water and all they knew was that this was the way they had always done it. In some cases there was evidence of a physiological difference, but it was difficult to say just how much or how important was the cold skill contribution.

Accordingly we planned a series of cold room laboratory studies (1) in which these same ten subjects were first examined and compared w th white groups in terms of manual dexterity and cold injury We used an instrument called the Craik screw plate which consists of a metal plate containing a series of concealed nuts. Screws are picked up and inserted into the concealed nuts in the plate.

We found that the Eskimo-Indian group showed a loss of 3 63 units under cold conditions, while the white group lost nearly twice that amount, i.e. 6 9 units.

Satisfied that there were basic differences in their manual ability in the

cold, we proceeded to administer a number of measures of sensory motor functions which are generally accepted to be components in the decline of manual dexterity. Of course we took temperature recordings of the index fingertip. We conducted measures of tactile sensitivity using Mackworth's V test, which is actually a two-point discrimination measurement. We recorded kinesthetic sensitivity, took a strength-of-grip test, and a joint flexibility test which was developed by Hunter (2) in connection with his work on the induction of stiffness in the inter phalangeal joint of the index finger.

These measures all indicated that the native groups were definitely superior to the white groups at comparable temperatures, the decline of each of these functions was, for the natives, about half as much as that reported by the white personnel. However, from other tests it was apparent that with the exception of kinesthetic sensitivity, which showed no change, all of the functions of native group began to decline when the temperature of the finger tip was between 12° C. and 9° C., which is approximately the same point at which decline in manual dexterity occurred.

A comparison of these two groups indicates that the superiority of the natives to the white is definitely a physiological thing, and that when separate functions begin to decline in the natives, manual dexterity also shows a deterioration. Although there may be some tricks of the trade used by the group, basically, the decline occurs when physiological changes take place.

It is interesting to note that the group showed considerably less decline in measurements of interphalangeal joint flexibility change. Hunter (2) has postulated that changes in joint stiffness in the fingers are due to a change in the viscosity of the synovial fluid at the joint, and he has demonstrated that this change is independent of cooling elsewhere, that is, the reduction in flexibility of the interphalangeal joint is independent of cooling at any other area than the interphalangeal joint itself. Our work seemed to confirm his findings, but in comparing the two groups under comparable conditions, the white group showed a decline of 12.25 per cent, whereas in the native group it was only 4 per cent.

Under more severe conditions, for example after two minutes exposure in ambient air at −35° C., the white personnel showed a decline of 28 per cent in joint flexibility, while the native group declined only 16.7 per cent.

In examining the finger temperature, we found that both the white and native groups eventually reached approximately the same skin temperature during exposures to −25° C. for a period of twenty min-

utes There was a sudden sharp drop at the beginning of the exposure, which seemed to be a bit more rapid in the Eskimo-Indian group than in the white group, but it was not significantly so The mean temperature over the period for the white group was 6.7 C., while for the Eskimo-Indian group it was 6.2 C. but the differences were not significant. After fifteen minutes of exposure, the temperature of the Eskimo-Indian subjects began to increase, but it followed the general pattern which was noted in the white group Their manual dexterity curve, and some of their skin sensitivity curves, are much flatter than the curve of the white group

I should say the decline in dexterity was much slower and much more gradual in the Eskimo-Indian group the white group began to show deterioration almost immediately and at a higher skin temperature.

Burton It is not because the native subjects keep up their tempera tures and so maintain their function it is that they can maintain their function at lower temperatures.

Coffey Exactly I think the lowest temperature we had them working at was —0 2 C. Their manual dexterity under those conditions had declined to something like 4 7 units, which still compares very favorably with the 2.6 reported at 9 C

The white subjects reported considerable pain at the ambient air temperature of —16° C. It was impossible to obtain a pain report from the natives I think they were so proud of their ability to operate in the cold that they may have failed to report accurately It was only after rapid cooling, at a wind chill of 1 500 for two minutes, that they would admit they were feeling what they described as a stinging sensation.

Brown How did the initial skin temperature of the natives compare with that of the white subjects?

Coffey That was a point we were very much interested in, Dr Brown In the Eskimo-Indian group we observed a slightly lower temperature, not consistently but on some occasions however it was not significantly lower than that reported from the white subjects We checked our figures against several different experiments that have been conducted in both the United States and Canada, and there still was no significant d fference in our group as compared with the whites

Blair What was the effect of repetition on the over-all performance? Do you have any data on the learning or training factors?

Coffey Other workers have demonstrated evidence of learning in one of the manual dexterity tests which is slightly different than the one we employed But we used subjects who had been trained in the warm temperature to a point where they were presumably as proficient as they could be. Based on, I think, ten replications, there was little, if any

evident improvement in the Eskimo-Indian group In the white group it was not possible to prolong the experiment that far and there are no data available.

Behnke The natives were not physiologically superior to the white subjects, were they?

Coffey Quite the contrary Our conclusion was that the superiority of the Indian Eskimo group applied only to their ability to withstand exposure and to perform far better than the white troops in low temperatures

Shumacher This is in spite of the fact that they had roughly the same heat loss and loss of temperature from the hands per unit of time of exposure?

Coffey Yes.

Burton Doesn t this remind you of the conduction of peripheral nerve where after exposure an increased resistance to cold block *in vitro* can be shown? In other words, these Eskimo-Indian subjects are not doing this as some of us might have thought, by maintaining a higher temperature of the finger through a cold-induced vasodilatation, called the hunting reaction It must be due to a change occurring in the nerves and the tissue itself

Carlson What was the incidence of frostbite in these groups?

Coffey The Eskimo-Indian group showed no evidence of frostbite or cold injury whereas in a previous white study it was 36 per cent. These were two experiments performed on a group of white personnel who had undergone a period of acclimatization for I think, two weeks, and who were then exposed to –25 C. for 20 minutes On each occasion 36 per cent in the first case I think, and 32 per cent in the replica, suffered minor frostbite and were withdrawn from the experiment.

Horvath Were these men in the nude or clothed?

Coffey They were dressed in environmental clothing, and the only exposure was the bare hand.

Horvath Dr Freedman and I (3) observed men at temperatures of –30 C. and –40 C. during similar tests, in which the subjects took bolts, and so forth apart Even in our poor white trash, we did not see this tremendous difference in response as compared with the natives. I think part of our group were Canadian soldiers and they seemed to do fairly well I am surprised at the tremendous difference you have observed.

Coffey I did not witness the experiment I mentioned, but I believe the demonstration was performed very carefully

Carlson Have you observed any changes which could be compared

with those of Mackworth (4)? He reported higher skin temperatures, did he not?

Coffey Yes, I believe so.

Burton You contradict his results in your experiments. He found that skill was maintained in large measure, by keeping the hands warm.

Coffey Mackworth's experiments were conducted under conditions of high wind, were they not? Our studies were all done in ambient still air

Brown Are you suggesting that all this was due to tissue adaptation?

Coffey I am afraid I cannot suggest.

Behnke It was psychological, if we can use that term.

Sellers Mr Coffey if the Eskimo-Indian group showed no evidence of frostbite, and their extremities cooled more quickly are you implying that their skin does not freeze at the same temperature as that of the white group?

Coffey Yes not at the same ambient temperature.

Sellers When the temperature goes down below zero the Eskimo-Indian group should show some evidence of frostbite.

Shumacker You said there was really no statistically significant difference in the rate of cooling.

Coffey No there was not.

P gé Is there any difference in the thickness of the stratum corneum?

Coffey We have not done any of these examinations. I think that is one area that should be thoroughly investigated.

Shumacker Was there any difference in the water content of the skin?

Carlson What was the time interval involved in the temperature drop?

Coffey I do not have this information in graph form. It was over a period of 20 minutes.

Behnke Perhaps the hands of the natives were calloused. Were the fingers more chubby than those of the white group?

Coffey There is a possibility that the hand tends to be more chubby Perhaps you have noticed that they have a fat, pudgy short appearance. But I believe they were no more calloused than the a erage soldier's hands would be.

Behnk How long had the white subjects been in the north one season or two?

Coffey Less than that six weeks at the most.

Blair Mr Coffey's results may be quite easily explained by referring to skin temperature cooling patterns. That the temperature of both Eskimo and white subjects declined in the same manner and to the same

level, with only one-third of the white group exhibiting frostbite, has been confirmed by animal experiments.

We subjected many rabbits to cooling procedures, using skin temperatures of the feet as the criterion of how severe the cold injury was. Within one hour the temperature of all rabbits was reduced in a similar pattern to sub-zero foot skin temperatures. After this initial cooling period of one hour some rabbits will develop severe frostbite after a further hour and-a half of cooling, although in other rabbits the procedure may be continued for an additional fourteen or fifteen hours without any cold injury whatsoever. The latter group show at regular intervals the hunting reaction as a rewarming and protective device.

Horvath The two groups were kept at the same temperatures?

Blair Yes, but the point is this just because the temperature of an area of skin cools down to zero centigrade, or even sub-zero, it is no indication of cold injury. Skin temperature may be held at a critical level for a period of an hour or for many hours without cold injury. But at some point the hunting reaction fails, skin temperature falls to near environmental temperature, and cold injury occurs. We have found the critical skin temperature level to be approximately −5 C. Cold-induced vasodilatation (hunting reaction) will rewarm the skin many times at temperatures down to −5 C but once skin temperature falls below that level, cold induced vasodilatation and subsequent rewarming never recurs. The length of time the skin is permitted to remain below −5 C determines the extent and degree of frostbite produced. All of these subjects would exhibit frostbite if their skin temperatures declined to a point much lower than 9 C.

Shumacker Mr Coffey has not recorded temperatures that low

Blair But if he should follow the temperature pattern in these individuals at levels below 9 C. even though the cooling pattern and temperature levels may be the same in the Eskimo and the white man, I am sure that the Eskimo would show a much more prolonged period of the protective hunting reaction than the white man.

Burton It may be that the native does not let his temperature fall to this critical point.

Blair Or the native's peripheral vascular mechanism may be conditioned to provide a very long period of physiological protection at low ambient temperatures which prevents the tissues from falling below the critical temperature level and becoming injured.

Shumacker It could still be a vasomotor phenomenon.

Behnke Deep tissue temperature is the real criterion.

Blair In these experiments of Mr Coffey's they did not go to deep tissue levels. His problem was to explain why with both the Eskimo and

white subjects cooled down to 9 C., one-third of the white subjects exhibited cold injury but none of the native subjects did. There is no discrepancy here if one considers the possible protective mechanisms of the two groups, and the possible previous cold adaptation of the native

Burton. In other words, although the temperature curves are identical down to 9 C., you believe they are not the same below that point?

Blair Yes.

Horvath Mr Coffey did you follow them below the critical level?

Coffey In the data I have reported here that was not done, but we have reduced the temperature to −0.2 C., without any evidence of injury

Shumacker You would not expect them to freeze at −2 C.?

Blair I have seen the temperature of human subjects in cold rooms repeatedly go lower than that without any skin injury and I have often reduced the temperature of animals to −5 C. without evidence of cold injury

Shumacker Colonel Blair says there may still be a difference in vasomotor response after prolonged exposure, but the performance tests were essentially the same, which must be explained as a difference in nerve conductivity or something of that sort, rather than on the basis of circulation alone.

Burch I should like to mention some experiments which may throw some light on this. We have attempted to freeze a local circular area of skin with a copper bar cooled to about 6 or 8 F It was not possible to control precisely the pressure of contact but we regulated it as well as we could A number of the subjects did not develop any freezing, even at the end of prolonged contact with the cold copper rod

In another experiment, we submerged an isolated leg of a rat in a freezing mixture and found that if the leg were covered with a lot of hair a little film of air was trapped between the hairs which acted as an insulation, and resulted in variation in the depth of cooling and freezing as measured with thermocouples in the leg There are probably various insulating materials on and in the skin, such as sebaceous material and lipids

Horvath. You are going back to the biophysical-biochemical phenomenon as opposed to the vasomotor I think I would agree that the biophysical and biochemical would be more important than the skin temperature changes.

Behnke How can you say biophysical at all, until we the real criterion deep skin temperature? There was a in Chicago who was exposed to freezing temperatures temperature of the skin on the back was that of the freezing but she had no frostbite of the skin in

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Horvath. You are going back to the biophysical-biochemical phenomenon as opposed to the vasomotor I think I would agree that the biophysical and biochemical would be more important than the skin temperature changes.

Behnke How can you say biophysical at all until we know? Isn t the real criterion deep skin temperature? There was a woman patient in Chicago who was exposed to freezing temperatures overnight. The temperature of the skin on the back was that of the ground, which was freezing, but she had no frostbite of the skin in that area The deep

temperature subdermally over the trunk was perhaps much higher than it was at some peripheral part of the body

Horvath That patient lost her legs.

Behnke Have you made studies of deep temperature in the feet of rabbits?

Burch. We measured the deep temperature of the rats in another experiment We severed the leg of the rat allowed it to reach ambient temperature, placed thermocouples at various depths in the leg, and submerged it in a freezing mixture All of the leg did not freeze. I think it has something to do with the amount of air which is trapped

Burton Mr Coffey s results on differences in manipulative skill measured at much higher temperature than these animal experiments, force us to a biophysical-biochemical explanation, because after all the sensory nerves involved are right in the top of the skin. It would indicate a difference in tissue. However in the case of cold injury that explanation may not apply it may still be a vasomotor difference.

Blair The biophysical concept would not explain why animals acclimatized to long periods of cold exposure become so remarkably resistant to cold injury As a matter of fact, we can almost immunize an animal against cold injury by previous maximal acclimatization to cold.

Shumacker It seems to me there still remains the possibility that it may be partly vasomotor because as Captain Behnke said, perhaps the group that performs well and has just as low a skin temperature as the other group that performs badly has a deep temperature which is higher We do not know about that at the moment.

Burton. The point is the receptors concerned with the manipulation are right at the surface, so this would not apply

Coffey Your argument is supported by the decline in temperature of the interphalangeal joint.

Brown We have done some blood flows on the Eskimos and on our control group of medical students Figure 13 shows the average hand blood flows at different water temperatures from 5 C. to 45 C. The hands were in the 5 C. bath for only 90 minutes in the case of the control group and for two hours in the case of the Eskimos, and we saw vasodilatation in the hands of the controls but very little in the Eskimos. The Eskimos maintained a higher blood flow at all times than was seen in the controls. In the forearm the curves were different and there was a dilatation at 5 C. in the Eskimos which did not occur in the controls. Also at 5 C. the deep muscle temperatures in the forearm of the Eskimos were lower than in the controls. The drop in blood flow with decreasing temperature is, on the average, about the same in the two groups

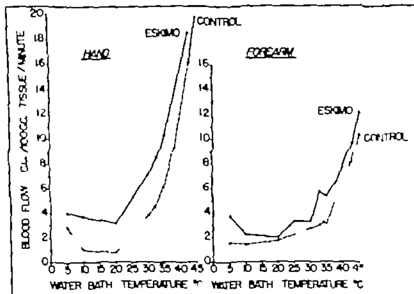


FIGURE 13 Average forearm and hand blood flow in controls and Eskimos in water baths at temperatures from 5 C to 45 C Reprinted, by permission, from Brown, G. M Bird, G S Delahaye, D J Green, J E Hatcher J D and Page J Cold acclimatization *Canad M A J* 70, 258 (1954)

The detail of events in the 5 C. water baths is shown in Figure 14 There is more fluctuation in blood flow in the Eskimo than there is in the white man at this temperature and the deep muscle temperature comes down much more quickly in the Eskimo than it does in the white man. We think this is due to the greater blood flow through the hand and the greater flow of cool blood in the venous system of the forearm

At 10 C. the results were different (Figure 15) At 5 C. the blood flow in the Eskimo came down rapidly to its lowest level but at 10 C. the hand blood flow in the Eskimo declined much more slowly than in the white man. Again, there was greater fluctuation in hand blood flow at all times as compared with the white man. Muscle temperature in the Eskimo was a bit lower at 5 C than it was at 10 C. Despite this low muscle temperature, we have the definite impression that there was a maintenance of manual dexterity which must have been dependent, in some degree, on events in the muscle of the forearm in the Eskimo It is our feeling that this was a dual thing in which there was evidence of tissue adaptation as well as difference in the vascular response in the two groups of subjects.

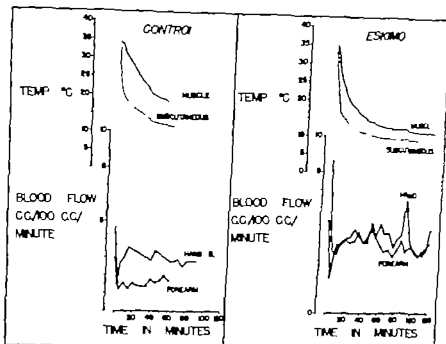


FIGURE 14 The average response of forearm, subcutaneous, and muscle temperatures, and forearm and hand blood flow in three controls and three Eskimos during immersion of hand and forearm in a 5 C. water bath. Reprinted, by permission, from Brown, G. M., Bird, G S., Delahaye, D J Green, J E., Hatcher J D and Page, J Cold acclimatization. *Canad M A J* 70 258 (1954)

Burton. I shall remind the group about tissue adaptation. If we take pieces of the bark of trees at different seasons of the year and put them in the refrigerator we find a difference in the degree of acute cold they will stand before the metabolism is changed.

Brown. Haven t the Scandinavians shown a change in the consistency of fat in the acclimatized person?

Horvath There has been a report recently on the iodine number

Brown. As you go down the leg of the animals who live in the north, there are changes in the iodine number of the fat in these tissues.

Horvath I do not think we can eliminate the vascular component in explanations of Mr Coffey s findings. We have a little more evidence for the biophysical-biochemical changes than we have for the vascular component.

Behnke What are the biophysical biochemical changes which would make for better adaptation to the cold

Burch Less water

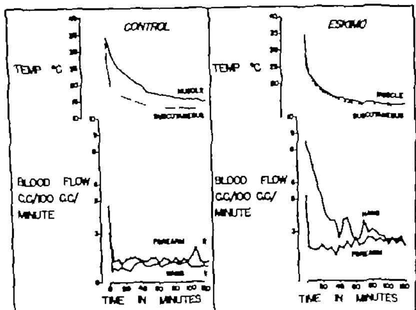


FIGURE 15 The effect of immersion of hand and forearm in water bath at 10°C. The results show were obtained on groups of five in the hand studies, and on four controls and five Eskimos in the forearm studies Reprinted, by permission, from Brown, G M Bird, G S Boag, T J Boag, L M Delahaye, J D Green, J E Hatcher J D and Page, J The circulation in cold acclimatization *Circulation 9 813 (1954)*

Burton In the case of the tree bark, there is a definite change, with the season, in the protein content The extraordinary thing is that in August when the temperature is still rising, the tree bark begins to be more cold resistant.

Blair It has been observed that as long as the peripheral vascular mechanisms are functioning efficiently no cold injury will occur and also that cold injury occurs only when this peripheral vascular function fails. Would you put that on a biophysical-biochemical basis?

We have repeated animal experiments which demonstrate that so long as the hunting reaction is present we can never get cold injury but when the hunting reaction fails there is always cold injury The degree of cold injury obtained depends upon how long the animal is exposed after the hunting reaction fails.

Horvath. I m afraid I am not a strong believer in the hunting reaction. After many attempts, I have not succeeded in finding it.

Blair We have never had an experimental animal exposed to cold

that has not demonstrated a very effective and very efficient "hunting phenomenon," namely a rhythmic cycle of cooling of the foot to near zero and sub-zero followed by sudden spontaneous rewarming of the skin up to as high as 20° C.

Horvath My subjects have always been human I cannot talk about the rat, rabbit, and dog

Blair Humans cannot be exposed to as low a temperature as rabbits.

Horvath I have had men cooled down so that the toe temperature was below 5° C for two to three hours in some cases, and sometimes longer without much evidence of injury

Burch How did you measure the temperature? Was a thermocouple placed in the skin?

Horvath I have done it both ways The thermocouples have been on top of the skin, or threaded through the upper layer of the epidermis.

Burch You measured the temperature of the interphase between tissue temperature and ambient temperature?

Horvath Yes I do not know of anyone who has not done that regardless of the method. The fact that it is pulled through the epidermis reduces that factor somewhat. I think there is stronger evidence that that temperature is more likely to be closer to the skin temperature, than is the temperature which is recorded with a thermocouple on top of the skin and underneath

Blair Thermocouples may be placed on the tip of the rabbit's toe on the base of the toe, at the ankle, and at various points along the foot. The thermocouple we use as the criterion for our cold injury experiments is the one at the base of the toes between the third and fourth metatarsophalangeal joints.

Shumacker There is good evidence from plant studies that water content influences the susceptibility to freezing

Horvath There was Barbour's work (5) on the rat in 1943

Burton Chatfield Lyman, and Irving's determinations (6) were unequivocal evidence of local tissue changes, and indicated that the nerve of a gull did conduct to a lower temperature after the bird had been exposed and acclimatized than it did before when it was kept in the laboratory

In some of the results Mr Coffey has told us about, it seems to me there was unequivocal evidence of tissue change, that is, biophysical biochemical adaptation. For instance, he stated that even though the temperatures were the same the joint stiffness varied.

Coffey The original work of Hunter (2) was done with reference to external skin-joint temperature. The temperature was taken at the surface of the joint.

Horvath. And in the joint?

Coffey No

Horvath Joint temperatures ha e been reported for some time (7) there is a great difference in these temperatures.

Coffey We have suggested that the native and white subjects show differences in deterioration. If this is due, as Hunter points out, to the mucin content of synovial fluid at the bursa, is there any method by which changes can occur during acclimatization?

Brown Isn t Hunter planning to use an animal large enough to enable him to obtain samples of synovial fluid from the joints?

Horvath That can be done in the rat. You can get enough out of the joint for microchemical analysis and also you can measure joint temperature. These measurements are relatively simple to make. They can be done in the finger joints as well as in the knee joints

Coffey Do you believe we would find a difference in the synovial fluid of the Eskimo for example?

Horvath I do not believe anything until I see the evidence

Shumacker Would not thermocouples in the joint interfere with joint mobility? Are these passive movements of the joints?

Coffey Actually Hunter s method was to reduce the temperature of the finger until he obtained a certain surface temperature. Then he required the subject to flex for a period of ten seconds.

Horvath I have had a thermocouple in my knee joint and I have walked for five miles with it in there

Burton I agree with Dr Shumacker that there is unequivocal evidence for biophysical-biochemical adaptation, and also for the importance of the vasomotor factor I do not quite see Colonel Blair s point of iew that only one is important

Blair I agree with you, Dr Burton, that both may be important, but to place a biochemical state as the predominant factor is definitely contradictory to the evidence we have The ascular evidence, at least in our experiments, is so impressive to us and to those for whom we have demonstrated it, that we feel it must be recognized at least as a very important factor

Horvath. Let us merely say that apparently both are invol ed, and that at the moment we shall *not attempt to decide which is the more* important.

Brown May they not be connected? May the amount of vasodilatation not be related to the biophysical state of the tissue?

Behnke Why not eliminate the vasomotor cut off the blood supply and repeat these experiments?

Blair We have done that. We have put tourniquets on these animals,

and then they all freeze in approximately the same period of time. On the other hand, if the vascular supply is left intact, there is great discrepancy in freezing times and freezing patterns.

Burton Then the rabbit does not have a biophysical adaptation.

Travell The flexibility of the interphalangeal joint does not depend only on the state of the joint, but also on the condition of the small muscles of the hand, the interossei and lumbricales. Shouldn t you measure, not only joint temperature, but also muscle temperatures in the hand itself?

Coffey It may well be that the method Hunter used for measurements was not sensitive enough, but he demonstrated that the joint flexibility decline was dependent on joint cooling alone, regardless of whether there was cooling at the joint, over the whole hand, or of the hand and wrist, there was no difference in flexibility This seems to suggest that the friction at the joint, due to the change in viscosity is the factor

To sum up I think the finding with which we are most concerned is the fact that the differences between the native and white subjects are definitely of a physiological nature, and cannot be attributed to anything psychological, such as work organization or efficiency in the cold.

There is one point I did not mention. We had thought there would be differences between the Eskimo the Indian, and the half-breed, in terms of the decline of manual dexterity and other functions. But on the basis of the present data, there was no evidence of any racial pattern emerging in any of the areas I mentioned.

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STUDIES OF FAT DISTRIBUTION AND RESPIRATORY QUOTIENT*

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PERHAPS I SHOULD start by saying that "Fat Distribution and Respiratory Quotient" are two separate ideas. I do not mean to imply that fat distribution affects respiratory quotients.

We have been interested for some time in the importance of the major nutrients in relation to adaptation to cold. As you know, protein is generally regarded as undesirable as a fuel for extra heat production in the cold. When it comes to carbohydrates and fat, the thinking is more divided. Dugal, Leblond, and Thérien (1) have reported that in rats, using as a basis the self-selection of the major nutrients, high-fat diets are preferable. Mitchell and his group (2), working on men, have found that high-fat diets are probably more beneficial in the cold than high carbohydrate ones and they suggested that this might be due to the fact that if we consume high-fat meals frequently throughout the day there may be a deposition of fat under the skin, and thereby an increase in peripheral insulation. We have made some studies of body fat distribution, and have compiled data dealing with body composition and organ weights.

The "Respiratory Quotient" part of the title of this talk refers to studies on intermediary metabolism. We have found, of course, as others have, that there is such a thing as biochemical adaptation or biochemical changes in rats adapted to cold. I do not know whether the nature of these changes is such as to affect the vascular mechanisms, or whether alterations in the latter affect the enzymatic systems.

We shall commence with the effect of diet on adaptation to cold and fat distribution (3). Table XXIV shows the basic rations used; they did not differ very much in subsequent experiments. There are two points I wish to bring out. The first is that they were not extreme diets by any means. The low fat diet contained 5 per cent fat, which is more than

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TABLE XXIV

Basic Composition of Rations

	Low Fat	High Fat
Casein	15 0	21 5
Shortening (Crisco)	2 5	25.0
Wheat germ oil	2.5	5.0
Corn oil	0	10.0
Mineral salts	4.0	5 7
Cellulose	2 0	2.9
Sucrose	74.0	32.5
	100.0	102 6
Fat content per 100 grams 5%		39%
Calories as fat 11.2%		62 5%

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adequate, and the high fat diet contained 33 per cent carbohydrate. It is far from being a ketogenic diet, even in man.

The second point is that we kept the protein level low namely 15 per cent on the low fat ration This would not be adequate for young growing rats but it was sufficient for the rats we used, which weighed about 300 grams. In the cold, where the food intake is doubled, the intake of casein, in absolute values becomes quite high.

Changes in body weights of these animals are illustrated in Figure 16 At room temperature, the high-fat group weighed more than the low fat group at the end of the experiment. In the cold there was a small loss in body weight in both groups on the first day or so at 8 C and then growth was resumed. At this point we lowered the temperature to 3 C., and kept it there until the end of the experiment.

The high-fat ration obviously did not improve resistance during the first stage of exposure to cold, but later on this group gained steadily on the other one, and the final difference in body weight is significant. Possibly of more interest are the changes in body composition, which cor

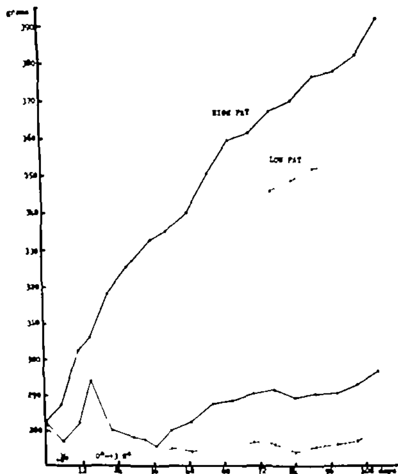


FIGURE 16 Effects of diet and exposure to cold on body weight in the rat

respond to the differences in body weight observed terminally (Table XXV)

Shumacker Were they isocaloric?

Pagé Yes, in the sense that the amount of protein, mineral salts, and vitamins, was the same in each ration on a calorie basis.

The gains in body weight at room temperature amounted to 96 gm. on the low-fat ration, and 129 gm on the high-fat ration, a difference of 33 grams. If we look at the total fat content, the difference is of the order of 29 grams. It is quite obvious that at room temperature, the

TABLE XXV

Changes in Body Weight and Fat Content with Diet and Environmental Temperature

	Room Temperature			Cold Room		
	Low fat	P	High fat	Low fat	P	High fat
Changes in body weight (gm.)	+96 ± 4 95	< 01	+129 ± 9 38	−5 ± 5 05	< 01	13 ± 4 16
Total body fat (gm.)	57 91 ± 3 39	< 01	87.20 ± 4 98	29.89 ± 1 71	> 05	33 97 ± 1 46
Fat content (% of body weight)	15 44 ± 0 81	< 01	20 98 ± 0.88	10 69 ± 0 54	>.2	11 58 ± 0 52
Skin fat	3 16 ± 0.21	> 4	3 39 ± 0 18	2 00 ± 0 14	> 1	2.28 ± 0 12
Skeletal fat	4.27 ± 0 17	< 01	5 27 ± 0.21	3 87 ± 0 13	> 5	3 99 ± 0 15
Adipose tissue fat	8 01 ± 0 56	< 01	12.32 ± 0 60	4.88 ± 0 31	> 3	5 32 ± 0 30

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animals on the high fat diet took more food and became obese. Some had as much as 150 gm. of fat. In the cold the difference in body weights between groups was smaller, but still significant. It was of the order of 18 gm., the animals on the high-fat diet being the heavier ones. Here the difference did not correspond to any deposition of fat. Of the 18 gm. of additional weight, only 4 gm. was fat, so we can conclude that in the cold the animals on the high-fat diet actually showed a larger growth of active tissues.

Fat distribution is expressed in Table XXV in percentages of body weight. We divided the fat into three categories: *skin fat* refers to the fat in the pelt; *skeletal fat* is that of the dressed carcass, including the lungs, heart, spleen, liver and kidneys; *adipose tissue* includes the scapular and pelvian fat belts, plus all the fat of the abdominal cavity.

At room temperature, the animals on the high-fat diets accumulated more fat, and the proportion of fat in each fraction was larger, as you would expect. The same was true in the cold, although the differences were not significant. As you know, when an animal desposits fat, it does so in preferred regions, such as the abdominal cavity. Consequently, as the animal becomes fatter, the percentage of the total fat in the different regions changes: it is lower in some and higher in others.

In order to arrive at a true estimate of fat distribution, involving a progressive increase in fat deposition, we are obliged to resort to regression lines, as shown in Figure 17. In abscissae we have the amount of total body fat in grams, and in ordinate the amount of fat in each fraction also in grams. The solid line represents the high fat group, and the

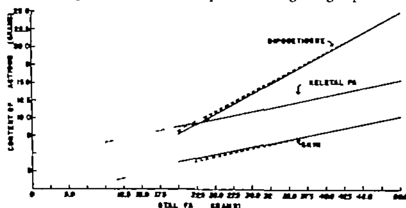


FIGURE 17. Fat distribution in a cold environment. Low fat diet ..... High-fat diet ——. Reprinted by permission, from Pagé, E. and Babineau, L. M. The effects of diet and cold on body composition and fat distribution in the white rat. *Canad. J. M. Sc. 31: 22 (1953).*

dotted one the low fat group It is quite obvious that the nature of the diet did not in any way influence the distribution of fat In fact, it is rather surprising that the two groups should overlap each other so well. These rats were kept in the cold

Figure 18 shows the same sort of thing for the rats at room tempera

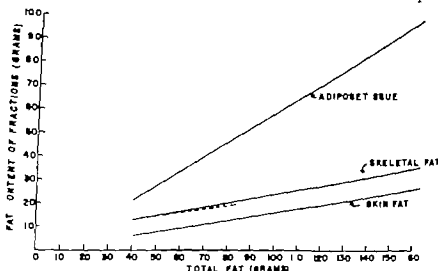


FIGURE 18 Fat distribution at room temperature. Low fat diet .... High-fat diet —— Reprinted, by permission, from Pagé, E., and Babineau, L. M The effects of diet and cold on body composition and fat distribution in the white rat. *Canad J M S* 31, 22 (1953)

ture The scale is reduced because the fat content is so much higher but if we were to plot the previous values on this graph, they would fall in line with the values for the low fat group Here, again, there was no significant difference between high-fat and low fat rations The trend, if any was toward a small proportion of the total fat under the skin on the high-fat ration. To conclude, there was no reason to believe that a high-fat ration would lead to a preferential deposition of fat under the skin.

Figure 19 shows the same values expressed in percentages of the total fat, for rats kept in the cold. The interest of this lies in the finding that with increasing fat content, the proportion found in the dressed carcass may drop from 65 to 30 per cent, while in adipose tissue it rises from 25 to 50 per cent. It follows that fat distribution expressed in percentages may be misleading when comparing rats of different fat contents.

Percentage values for rats kept at room temperature are illustrated in Figure 20 One point of interest is the fact that the skin fat represents

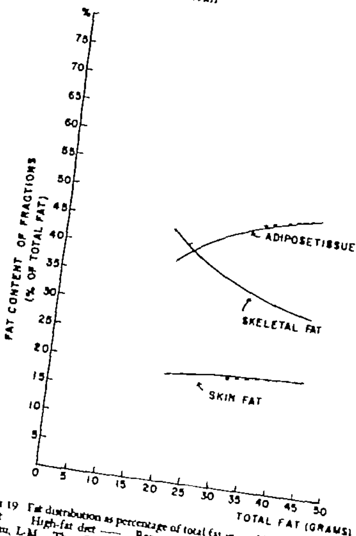


FIGURE 19 Fat distribution as percentage of total fat in cold environment. Low fat diet .... High-fat diet ——. Reprinted, by permission, from Pagé, E., and Babineau, L-M. The effects of diet and cold on body composition and fat distribution in the white rate. *Canad. J. M. Sc.* 31: 22 (1953).

a constant percentage of total fat over a very wide range particularly in the low fat group. This may lend weight to the measurement of skin fold thickness as an index of body fat.

We measured food utilization in the same animals over a limited period. Actually it was 38 days in the cold, and 28 days at room tem-

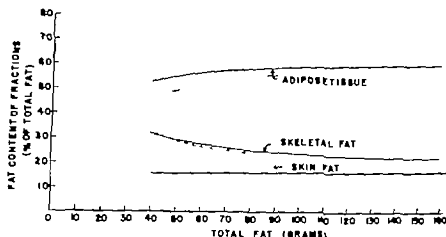


FIGURE 20 Fat distribution as percentage of total fat at room temperature. Low fat diet ...... High fat diet ——. Reprinted, by permission, from Pagé, E., and Babineau, L. M. The effects of diet and cold on body composition and fat distribution in the white rats. *Canad J M Sc* 31 22 (1953)

perature During that period, changes in body weight were the same in both groups at a given temperature (Table XXVI)

The food intake is expressed in calories per day per kilogram of body weight, and finally per square meter of body surface. On the latter basis we observe that the food was utilized a little more efficiently on the high-fat ration at both environmental temperatures. Forbes and his co-workers (4) did some very precise measurements of the efficiency of food utilization at different levels of dietary fat, and they arrived at similar values when comparing low fat to high-fat rations. These authors suggest that in high carbohydrate diets the higher energy expense of food utilization is caused by the synthesis of fat from carbohydrate.

Table XXVII shows the liver weights of these same animals. When we discussed this earlier it was suggested that on a high protein diet the liver was larger We found that livers were larger on the low fat ration at either temperature, and larger in the cold than at room temperature.

Birch What type of fat did you use?

Pagé A mixture of wheat germ oil corn oil, and shortening (Crisco)

Behnke Those percentages are in terms of gross body weight they are not absolute liver weights are they?

Pagé Absolute liver weights are also shown in Table XXVII The rats at room temperature weighed about 100 gm. more, so we must express liver weights on a body-weight basis to obtain a clear picture

TABLE XXVI

Caloric Intake on Different Diets and at Different Temperatures

	Room Temperature			Cold Room		
	Low Fat	P	High Fat	Low Fat	P	High Fat
Period of measurement (days)	28		28	38		38
Average body weight (grams)	356		378	277		291
Average gain in body weight (grams)	21		21	0		1
Caloric intake						
Cal per day	63 0 ± 97	> 6	62.1 ± 1 97	102 ± 1 42	> 3	100 ± 1 74
Cal /100 gm. B W /day	17.8 ± 91	=.2	16 5 ± 39	36.9 ± 70	< 01	34.3 ± 45
Cal./m²/day	1480 ± 18	=.05	1404 ± 34	2782 ± 41	<.01	2641 ± 35
Increase in caloric intake on low fat ration (%)	5 4			5 3		
Increased intake in the cold (%)				88		88

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TABLE XXVII

Liver Weights in Relation to Diet and Environmental Temperature

	Initial Control Group	Room Temperature			Cold Room		
		Low Fat	P	High Fat	Low Fat	P	High Fat
Livers							
Fresh weight (gm.)	9 60 ± 34	13 69 ± 33	> 3	13 15 ± 40	13 13 ± .29	> 3	12 19 ± 30
% Total body wt.	3 39 ± 09	3 68 ± 06	< 01	3 19 ± 05	4 73 ± .09	< 01	4.13 ± 07
% Fat free body wt.	3 68*	4 35 ± .08	< 01	4 05 ± 08	5 30 ± 10	< 01	4 67 ± 08

*Total body fat estimated from perirenal fat (Figure 21)

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On a fat free basis which we have also calculated, we obtain truer values because the active tissue mass is not diluted with excess fat

This experiment dealt with rats on either a high- or low fat ration, and a rather low-protein level We next doubled the protein intake on the high-fat ration, just to make sure that there was no advantage to be gained from a luxus consumption of protein. There was no difference in body weight gains, either at room temperature or in the cold (Table XXVIII)

TABLE XXVIII

Effect of Diet and Environmental Temperature on Body Weight Changes in the Rat
(Average initial body weight: 295 gm. for all groups)

	Number of Rats	Final Body Weight (gm.)	Changes in Body Weight (gm.)	Significance of Differences Between Groups (P)
Room temperature				
Medium protein	29	440 ± 13.4	145 ± 7.1	> 6
High protein	29	436 ± 9.0	141 ± 7.2	
Cold room				
Medium protein	24	290 ± 7.9	−5.5 ± 4.4	> 4
High protein	20	295 ± 7.0	−1.0 ± 4.0	

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I should like to point out that in the previous experiment the rats took about four months to regain their original body weight At the time of sacrifice they were in very good condition, with sleek fur and few instances of tail necrosis In the present case, the rats regained their original weight in only 75 days they had the same initial body weight as the others, but their final condition did not appear to be as good. Here we determined body composition in terms of fat water and fat free dry matter, thinking that possibly there might be a partial replacement of water by fat in the cold.

TABLE XXX

Correlation Between Total Body Water and Fat Free Body Weight

	Correlation Coefficient r	Regression Line Value of Y	Standard Error of the Slope	Standard Error of the Estimate	
				In Grams	In % of the Mean
Initial control group	0 984 ± 04	0.818X — 26 07	± 035	3 12	1 75
Cold room, high fat.					
Medium protein	0 976 ± 05	0 682X + 8 60	± 033	5 37	2.08
High protein	0 991 ± 03	0 678X + 8 52	± 021	2 91	1 56

X = Fat free body weight Y = Total body water

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Pagé I do not know It has only been measured on portions of pure adipose tissue.

Behnke That would mean the dry material would be less. If the water percentage were higher the percentage of dry material, that is protein and mineral matter would be less.

Horvath Lowry (6) and other experimenters, have not been able to demonstrate that in a rat, weighing roughly from 200 to 300 gm., there is much of a change in the fat free body water

Pagé That is why I am a little wary of these results. In fact, the rats in the cold appear more normal than the ones at normal temperature. Perhaps we did not have a good sample

As we have seen, the fat content of animals killed initially is the same as that of cold-adapted rats killed later Water content is also the same So there is no clear indication, except from the questionable slope, that there is a change in water content with adaptation to cold At different times, we have also measured the perirenal fat as an indication of the total fat content.

Figure 21 shows the correlation between perirenal and total fat in three groups of rats. One is the initial group of the present experiment (*AA*) the second group (*BB*) is the low fat group of the first experiment and the third group (*CC*) is the high-fat group of that same experiment. Line *D* refers to the three groups combined, from which we derived the formula shown in Table XXXI.

As you can see the lines follow each other very closely which indicates that perirenal fat is a fairly good index of total fat Actually the coefficient of correlation is of the order of 0 96 for the three groups combined.

I should now like to show a few data regarding perirenal fat at the beginning and at the end of exposure to cold (Table XXXI) If we look at the last two columns on the right, we can see that where we measured total fat as well as perirenal fat there was very good agreement between the estimated and measured values Series *A* refers to the last experiment and as mentioned before the cold-adapted animals were no fatter nor were they leaner than the controls sacrificed initially In series *B* we are dealing with the previous experiment Unfortunately we did not measure total fat in the controls but on the basis of perirenal fat the cold-adapted animals appear to have grown fatter although in one instance they actually weighed less The last set of data refers to much smaller animals, some of which were kept at 14 C., a much milder environment Here growth was as good in the cold as at room temperature, but the fat content was appreciably greater in the cold Thus, we have in series *B* what appears to be a partial replacement of

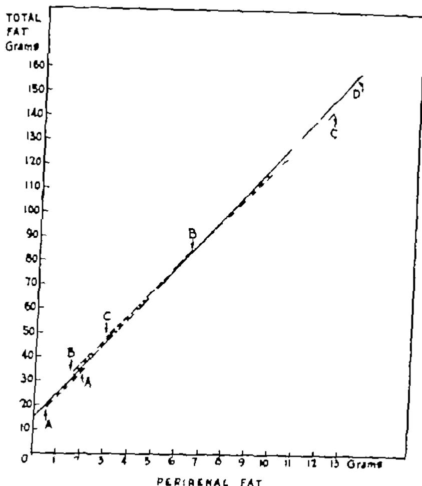


FIGURE 21 Correlation between perirenal fat and total fat. *AA* fox chow *BB* low fat diet *CC* high-fat diet Line *D* three groups combined Reprinted, by permission, from Pagé, E and Babineau, L M The effects of diet and cold on body composition and fat distribution in the white rat. *Canad J M Sc* 31, 22 (1953)

water or other constituents by fat, and in series *C* a preferential deposition of fat partially at the expense of active tissue growth.

These are very sketchy data and I am presenting them only to stimulate discussion. I remember Dr Burton's experiment in man (7) in which it was found that the caloric intake during the first few days of exposure to cold was much larger than the caloric output. On the basis of water balance and body weight I believe he suggested at the time that

TABLE XXXI

Perirenal Fat and Exposure to Cold

Groups	No of Rats	Temperature (C)	Experimental Period (days)	Average Body Wt (gm.)	Perirenal Fat (gm.)	Total Body Fat (gm.)	
						Estimated	Measured
(*A*) Initial controls	20	N	0	295	1.17	27.7	26.5
Medium-protein-high-fat diet	24	3	75	290	0.86	24.4	24.1
High-protein-high-fat diet	20	3	75	295	1.06	26.5	26.6
(*B*) Initial controls	20	N	0	282	0.78	23.5	—
Low fat diet	25	3	120	277	1.19	27.9	29.9
High-fat diet	26	3	120	295	1.79	34.3	34.0
(*C*) Initial controls	14	N	0	113	0.43	19.7	—
Final controls	14	N	29	158	0.41	19.5	—
Cold-exposed	12	14	29	160	0.76	23.3	—

Total Body Fat = 10.77 X + 15.11 (X = perirenal fat.)

this might happen through replacement of water by fat originating from extra food intake

We have no further findings, as yet, in connection with fat distribution and body composition. The only conclusion we can draw is simply that exposure to cold and changes in diet do not affect fat distribution any effect of a high-fat ration on body insulation results from a possible increase in total fat, and not from a different and thermally more efficient distribution of that fat.

We turn now to intermediary metabolism. We felt that if a high-fat ration was more beneficial in the cold, it might be because cold-adapted rats burn fat preferentially We thought a study of respiratory quotients might yield some useful clues (8) We used the Haldane open-circuit gravimetric method. Measurements were made either at 29 or at 5 C over a period of two hours. Table XXXII gives the pattern of the experiment We compared rats adapted to low or high fat rations, and adapted, or not adapted, to cold. The rats were fasted for 26 hours at

TABLE XXXII

Average Body Weights (in grams)
at Time of Respiratory Quotient Determinations

Low fat diet	Fasting	Maltose	Oil
29 C, Not adapted	166 (10)	215 (19)	204 (18)
Adapted	258 (15)	254 (21)	255 (21)
5 C, Not adapted	156 (13)	204 (17)	204 (16)
Adapted	261 (12)	244 (18)	246 (18)
High fat diet			
29 C, Not adapted	207 (15)	185 (15)	184 (16)
Adapted	188 (15)	183 (15)	189 (15)
5 C, Not adapted	208 (15)	183 (17)	185 (17)
Adapted	186 (15)	173 (16)	189 (14)

Number in brackets indicates the number of animals per group.

Reprinted, by permission, from Pagé, E., and Chénier L P Effects of diets and cold environment on the respiratory quotient of the white rat. *Rev canad de biol* 12 530 (1953)

room temperature, even in the case of the animals living in the cold. We felt, as does Dr Sellers, that prolonged fasting in the cold would stress them unduly The number in brackets refers to the number of determinations they were made on different animals for a given experiment, although the same animals were used both in the fasted or fed state. In the latter instance the rats were given either oil or maltose by gavage one hour before the R.Q determinations were made.

Horvath Why did you use maltose?

Pagé We felt we might have a more sustained absorption if there were some digestive work involved, and particularly less osmotic disturbance I realize now it would not have made much d fference

Adaptation consisted of exposing the rats, for three weeks or more, to an environment of 8 to 10 C., which was higher than the one we used before. There were two reasons for this first, there was no cold room available at a different temperature second, at this temperature the initial phase of body weight loss, which is a serious stress and may lead to occasional deaths was eliminated By exposing the rats to 10 C. only we avoided this factor and still obtained adaptation

Table XXXIII shows the respiratory quotients measured at 29° C. in

TABLE XXXIII

Effects f Diet, Test Meals, and Adaptation to Cold, on the Respiratory Quotients of Rats at 29 C.

	Fasting		Maltose		Oil	
Low fat diet	R Q	S.E.	R.Q	S.E.	R Q	S.E.
Not adapted to cold	0 752	006	0 952	016	0 746	.005
P	< 01		4		<.05	
Adapted	0 725	005	0 970	.012	0 733	.003
High fat diet						
Not adapted to cold	0 722	006	0 837	011	0.731	007
P	.2		< 05		3	
Adapted to cold	0 709	006	0 858	.014	0 717	.009

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rats on either diet, and adapted, or nonadapted to cold. All values fall within the accepted range, the lowest being 0 709 and the highest 0 970

If we first look at the effect of feeding, we find, as might be expected, that a sharp rise in the R.Q occurred following the administration of maltose from 0 752 to 0 952 and from 0 725 to 0 970 and so forth. On the other hand, the oil had no significant effect on the R.Q and we presume that the absorbed fat was deposited without being appreciably transformed.

If we go on next to the effect of the diet itself we see that the R.Q s were always lower in the high fat group for a given treatment. The values underlined are those where the difference between diets was statistically significant It is not significant between 0 725 and 0 709 for instance, probably because the low fat diet values were quite low so there was not much leeway for a further significant lowering to take place.

I must say that this finding is completely in accord with those of Samuels and his co-workers (9) Using different criteria they reported that animals burn preferentially the foodstuff which predominated in the previous diet That accounts, I imagine, for the consistently lower R Q s of the rats adapted to the high fat ration.

If we move on to adaptation to cold which is the main purpose of this work, we find in the fasting animal, and in those given oil, a lower R.Q in the adapted animals The differences are significant for the low fat groups, i.e 0 752 compared with 0 725 and 0 746 compared with 0 733 They are not significant in the high-fat groups although the changes are in the same direction. Here again control values are low enough so that there is not much chance to demonstrate a further lowering of any magnitude. If we look at the figures for the maltose-fed animals, after adaptation, we see the reverse. The values are always higher in the adapted animals, and the rise from fasting values is significantly greater in the adapted rats, in every instance and irrespective of diet.

When one has such unsupported figures as these for the R.Q they may easily lend themselves to contradictory interpretations We might argue, for instance, that the animals burn carbohydrates preferentially after adaptation to cold and as a consequence will deplete their glycogen stores more exhaustively during fasting because they will have no choice but to burn fat at the time of the R.Q determination. Likewise, burning carbohydrates preferentially they will show a higher R.Q following glucose absorption. That is one way to look at these data. We might also adopt the opposite view that animals adapted to cold burn fat preferentially so they have a lower R.Q in the postabsorptive state.

Following the administration of maltose, they may be transforming glucose into fat more quickly hence the greater rise observed.

We thought this should be checked, and we have measured fasting glycogen values in rats adapted to cold and also glucose absorption. Before going in to that however I should like to show you the R.Q s at 5 C. for these animals.

Crismon Dr Pagé what does the R.Q of the process of conversion of fat to carbohydrate amount to?

P gé In an animal that is doing nothing but converting sugar into fat?

Crismon No converting fat to carbohydrate

Pagé That would be below 0 7

Horvath 0 66-0 50

Pagé There is a great deal of argument about the transformation of fat into carbohydrate, but there is more and more evidence of gluconeogenesis from fat, and it is a good point to bear in mind

We have here (Table XXXIV) the R.Q alues at 5 C In the fasting state or following the administration of oil, we obtained absolutely

TABLE XXXIV

Effect of Diet Test Meals, and Adaptation to Cold, on the Respiratory Quotients of Rats at 5 C.

	Fasting		Maltose		Oil	
Low fat diet	R.Q	S.E	R Q	S E.	R.Q	S.E.
Not adapted to cold	0 699	.002	0.814	.006	0 699	.002
P	3		<.01		.8	
Adapted to cold	0 693	003	0.865	.007	0 698	002
High fat diet						
Not adapted to cold	0 686	.003	0 756	010	0.683	004
P	1.0		<.01		3	
Adapted to cold	0.686	003	0 801	008	0 690	004

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minimal values indicative of the exclusive oxidation of fats. This was in accord with the previous findings of Kayser on rats (10) hamsters (11) and guinea pigs (10 11 12) His observations were perhaps more conclusive in the sense that he measured the R.Q over three consecutive two-hour periods the center one being either 29 or 10 C., and the outside ones the other temperature In that way he was able to show a lowering of the R.Q in the cold, and a rise at 29 C.

If we are to interpret literally the lowest values obtained (0 683 and 0 686) it must mean that there is some conversion of fat into carbohydrates However an experimental error of 0 015 is not unusual in such determinations and I should hesitate to draw any conclusions on that point.

Following gavage with maltose we found the same thing as at 29 C. there was a larger rise in the cold adapted animals In summary observations made at 5 C. confirmed those at 29 C., with respect to maltose, while in the fasting state the R.Q s were just as low as they could be in all cases.

Table XXXV shows the effects of these treatments on the metabolic rates These are expressed in calories per square meter per 24 hours, taking into account the caloric value of the oxygen consumed at different R Q s

Burton What did you do between the total R.Q and the nonprotein R.Q ?

Pagé I ignored the protein R.Q

Burton. You assumed that was a constant proportion?

Pagé Yes. At 29 C., the metabolic rates are uniformly higher in the adapted animals, and with one exception these differences are significant. The differences are not as large as those reported by other authors, possibly because we used a higher environmental temperature in the cold namely from 8 to 10 C., instead of near zero

I might add that we measured the activity of these animals being tested for metabolic rate, and found, as you might expect, that fasting animals are restless they turn around in the cage, scratch themselves, and otherwise increase their activity whereas following a heavy dose of sugar or oil, they seem to be lulled into a pleasant dozing state, and are much quieter We cannot expect a rise in caloric output following maltose administration which would represent the energy expended in digestive and absorptive work I think it would be quite impossible with rats

In the cold, the energy output is roughly doubled this finding is in line with other work For some unknown reason, it is significantly lower in the adapted animals in the fasting state and on the low fat

TABLE XXXV

Effects of Diets, Test Meals, and Environmental Temperature, on the Metabolic Rate of Rats Adapted, or Not Adapted, to Cold

	Fasting		Maltose		Oil	
Low fat diet	Calories*	S.E.	Calories	S.E.	Calories	S.E.
29 C., Not adapted	1025	36.0	1011	27 4	1007	25 9
P	0.2		< 05		< 01	
Adapted	1095	27 4	1145	31 7	1155	27 4
5 C Not adapted	2243	38 9	2184	41.8	2133	44 6
P	0 9		<.05		>.05	
Adapted	2252	38.9	2318	46.1	2245	36.0
High-fat diet						
29 C., Not adapted	1040	21 6	1070	27 4	919	31 7
P	<.01		< 01		<.01	
Adapted	1130	24 5	1169	24 5	1143	20 1
5 C. Not adapted	2300	28.8	2243	31 7	2182	41.8
P	<.02		9		3	
Adapted	2107	30.2	2251	33 1	2127	28.8

*Calories per square meter per 24-hours

diet but because of the activity factor I do not think we should attach too much importance to this difference

I must say that we were primarily interested in R.Q. changes and I would not like to argue one way or another as to changes in heat production in the cold following adaptation

Sellers What kind of oil was used?

Page It was Mazola Oil, i.e., corn oil

To summarize this part of our work, adaptation to cold in the animal leads to lower R.Q.s in the fasting state and to higher R.Q.s in the process of absorbing carbohydrate To see whether this was due to preferential use of fat or of carbohydrate, we measured fasting glycogen in rats under similar conditions, and also glucose absorption.

Table XXXVI gives glycogen values in animals fed a high-fat, or low fat, ration at room temperature and in the cold also shown are the body weights which are quite similar and the liver weights. As we have seen before there is an increase in liver weight in the cold. Livers are also larger in the cold on the low fat ration than on the high fat ration

Samuels and his group (9) whom I mentioned before, have shown that in rats kept on a high fat ration, the nonfasting liver glycogen is lower than on a low fat diet, but higher in the fasting state. We can therefore assume that at room temperature liver glycogen would be higher on the low fat diet After fasting, we have on the high-fat ration a residual liver glycogen amounting to 20 mg per 100 gm of body weight, which is the same value as Samuels reported. Incidentally all rats were fasted at room temperature as previously

We know from Dr Sellers work, that in the nonfasting state, liver glycogen is higher at room temperature than in the cold. Following fasting, we found that the liver glycogen was 10 4 mg in cold-adapted, low fat animals instead of 3 4 at room temperature, which is three times as much a significant increase. I think we can assume that animals adapted to cold maintain liver glycogen slightly better during fasting and consequently that the lower R.Q s in adapted animals are the result, not of a lack of glycogen, but of a preferential utilization of fat (since the R Q is lower in adapted rats in spite of a higher glycogen reserve)

Finally we have the muscle glycogen. There is no significant difference between any groups at any temperature there is merely a slight tendency for the values to be higher in the cold, i.e. 509 compared with 557 and 564 compared with 581

Crismon Dr Pagé, have you any figures showing actual measurement of nitrogen excretion in these groups?

Pagé No I have never measured it

Sellers We have data on that, Dr Crismon.

Crismon Does it change in the cold?

Sellers There is an increased excretion of nitrogen, as soon as the animals are placed in the cold, regardless of whether the amount of food offered is increased or not. I assume the increased excretion is because of the stress of the cold, but because of the cold the animals condition deteriorates if a larger amount of food is not given.

If the animal is then fed *ad libitum* instead of the same amount it was taking at room temperature, one finds that there is a secondary increase in nitrogen excretion which may be as great as the initial rise observed on putting the animal in the cold After equilibrium has been established, and the proportion of fat in the diet is varied, it is observed that the nitrogen excretion is governed principally by the amount of

TABLE XXXVI

Effect of Adaptation to Cold on Fasting Glycogen Values in Rats Fed a High- or a Low Fat Ration

	High Fat Ration			Low Fat Ration		
	Room Temperature	P	Cold Room	Room Temperature	P	Cold Room
No. of rats	15		15	15		14
Body weight (gm.)	323		306	319		278
Liver weight mg./100 gm. B.W	2 39 ± 0 04	<.01	2 78 ± 0.01	2.45 ± 0.07	< 01	3 10 ± 0.06
Liver glycogen mg./100 gm. liver	857 ± 112	>.05	619 ± 61	138 ± 26	<.01	330 ± 56
mg./100 gm. B.W	20 4 ± 2.75	> 4	17.8 ± 1 72	3 4 ± 0 67	<.01	10 4 ± 1.84
Muscle glycogen mg./100 gm. muscle	509 ± 22	> 2	557 ± 32	564 ± 32	>.6	581 ± 22

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nitrogen taken in. Therefore, on a high fat diet, in which the percentage of protein is kept the same as on a low fat diet because the animal takes in less nitrogen, it excretes less nitrogen.

Pagé If the protein level is adjusted to the caloric content of the ration, for a similar number of calories consumed the animal obtains the same amount of protein

Sellers The only way it can be adjusted is by adding some inert material If we do not add celluflour or something of that nature to the high-fat diet the caloric intake is higher for the same amount of food. In my experience, the caloric intake is the greatest single factor governing the amount of food consumed. Therefore, on a high-fat diet, undiluted with inert material, the excretion of nitrogen is less than on a low fat diet.

Pagé It is larger because the caloric intake is slightly higher We have a low fat ration with, say 15 per cent protein *by weight* which is the level I used On the high-fat ration I raised the protein content to 22 per cent, so that each time a rat took 100 calories it consumed the same amount of protein, irrespective of the fat content of the ration. If they take more on the high-fat ration they are going to consume more casein as well I do not think our diets are comparable

Sellers You have changed the protein percentage in the diet you should keep it the same

Crismon The question I raised has to do with the matter of the R.Q I think Drury's studies (13 14) are important in this relation. He showed that a far greater proportion of protein is potentially convertible to carbohydrate than the fixed 58 per cent of protein formerly thought to be converted. In other words, on material balance studies in diabetic dogs, Drury was able to demonstrate that virtually all of the calories fed in the form of protein could be accounted for as metabolized or excreted carbohydrate If the fraction of protein being converted to carbohydrate is a variable feature of intermediary metabolism, then it seems unsound to ignore the nitrogen excretion on assumption that it is fixed and always bears a constant relationship to the total amount of carbohydrate

Pagé That is quite true. There is no direct evidence here to discard the protein metabolism and consider only the fat and carbohydrate *But* there is this point I know of no evidence that in the cold there is a greater requirement for protein in fact, it is the other way around.

Mitchell's work in man (2) has shown that increasing the protein content has a depressing effect on resistance to cold. We are not led to believe that adaptive changes are due to increased conversion of protein to carbohydrate.

Crismon Except that the difference in liver glycogen might be, in part, owing to the different rate of conversion of protein to carbohydrate.

Pagé That has been shown with high-protein diets as well. One observes this phenomenon of a higher liver glycogen on a high-protein diet in the fasting state.

Crismon As glyconeogenesis of protein proceeds at a greater rate, doesn t the R.Q change?

Pagé I suppose if the protein were transformed to carbohydrate, it would lower the R.Q which is the same effect that we have observed here.

There is one last point in connection with the fasting glycogen values we have measured glycogen in bears. They are not true hibernators they move around. The bears were in a wooden house, well caged in, and with no access to food. After I think, a three-month fast, we found that the liver glycogen was of the order of from 2 to 4 per cent for the group of three bears One may wonder how they can retain such a high glycogen content after living so many months without eating the fat stores were still quite high Unless they had preserved the initial glycogen without utilizing it for so many months, which is hard to believe they must have transformed either protein or fat into carbohydrate.

Horvath. It may be observed in certain insects if they are fasted, and they start off with a high fat content, the fat gradually disappears If they are starving, it is converted into carbohydrate then there is a gradual increase in carbohydrate and a decrease in fat.

Pagé That is, a progressive transformation of fat into carbohydrate Is that fairly well accepted?

Horvath I do not think it is well accepted, but at least there is evidence there, and further investigations should be made. I have a tendency to believe it can be done, myself

Barton. I believe there is some very old evidence (I have forgotten the reference) with regard to plants.

Horvath. The castor oil bean is one example.

Barton. In cold climates it is very much favored that is in the old French literature.

Pagé I think Bacchus (15) suggested that gluconeogenesis from fat under the influence of cortisone is stimulated by large doses of ascorbic acid

Table XXXVII returns us to high- and low fat rations. We have started measuring glucose absorption in animals adapted to cold, but so far have used only animals on a high-fat ration (16) As you know the absorption rate of glucose is less than on a high-carbohydrate ration.

nitrogen taken in. Therefore, on a high-fat diet, in which the percentage of protein is kept the same as on a low fat diet because the animal takes in less nitrogen, it excretes less nitrogen.

Pagé If the protein level is adjusted to the caloric content of the ration, for a similar number of calories consumed the animal obtains the same amount of protein.

Sellers The only way it can be adjusted is by adding some inert material. If we do not add celluflour or something of that nature to the high-fat diet the caloric intake is higher for the same amount of food In my experience, the caloric intake is the greatest single factor governing the amount of food consumed. Therefore, on a high-fat diet, undiluted with inert material, the excretion of nitrogen is less than on a low fat diet

Pagé It is larger because the caloric intake is slightly higher We have a low fat ration with, say 15 per cent protein *by weight* which is the level I used On the high fat ration I raised the protein content to 22 per cent, so that each time a rat took 100 calories, it consumed the same amount of protein irrespective of the fat content of the ration. If they take more on the high-fat ration they are going to consume more casein as well I do not think our diets are comparable.

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Pagé That is quite true There is no direct evidence here to discard the protein metabolism and consider only the fat and carbohydrate But there is this point I know of no evidence that in the cold there is a greater requirement for protein In fact, it is the other way around.

Mitchell's work in man (2) has shown that increasing the protein content has a depressing effect on resistance to cold. We are not led to believe that adaptive changes are due to increased conversion of protein to carbohydrate.

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Table XXXVII returns us to high and low fat rations We have started measuring glucose absorption in animals adapted to cold, but so far have used only animals on a high-fat ration (16) As you know the absorption rate of glucose is less than on a h gh carbohydrate ration.

TABLE XXXVII

Effect of Adaptation to Cold on Glucose Absorption in Rats Fed a High Fat Ration, and Average Body Weights of the Animals at the Time of the Determinations

		Room Temperature Animals	P		Cold Room Animals
Glucose Absorption					
(mg /100 gm. B W /hr)					
One hour period		88 ± 5 53	< 01		140 ± 13 11
Three hour period		82 ± 8 18	< 01		146 ± 7 13
Combined		85 ± 4 73	< 01		143 ± 6.99
Body weight (gm)					
One hour absorption	(10)*	395 ± 11 3	< 02	(11)	344 ± 10.2
Three hour absorption	(10)	381 ± 7 4	<.01	(11)	299 ± 9 5
Combined	(20)	388 ± 6.8	<.01	(22)	322 ± 8 4

No. of animals per group.

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I should like to mention Sinclair s work (17) at Kingston, in 1941 on the glucose absorption in rats fed high- or low fat rations.

Horvath What is your technique on absorption?

Pagé We use the classical Cori method with very minor modification. At room temperature, we measured the sugar absorption at one hour and three hours after gavage to correspond to the time periods used in the R Q measurements previously There were ten rats in each group At room temperature, after one hour the absorption rate was of the order of 88 mg per 100 gm. of body weight per hour and after three hours, 82

Incidentally Sinclair obtained a value of 100 for animals on the high-fat ration. In the cold, the absorption rate after one hour was 140 mg., and after three hours, 146 mg Again a very close agreement. If these

values are combined, we see that the absorption rate goes up from 85 to 143 mg when the animals are adapted to the cold. So again I suspect that after giving maltose to rats adapted to cold the high R.Q. was due to the fact that they were absorbing sugar at a higher rate, and probably utilizing it more quickly. I have no evidence as to whether this higher rate of glucose utilization after adaptation means faster oxidation, or simply a faster transformation into fat. I believe the latter is more likely.

Table XXXVIII shows measurements of glycogen depositions in these same animals after they had been absorbing glucose. The total liver glycogen one hour after absorption did not differ appreciably from the fasting value. After a three-hour absorption period, there was, of course, a larger rise. The amount of glucose absorbed, which was transformed into liver glycogen, was low: 5.2 and 7.8 per cent. These values are comparable to those reported by Cori (18) for animals having absorbed such small amounts of glucose. There is no evidence here of any difference in liver glycogen deposition as a result of adaptation to cold.

We have studied the brown adipose tissue which we find between the shoulder blades of rats (19). Table XXXIX shows the fresh weight of this tissue in controls killed initially and in groups of rats fed a low or a high-fat ration at room temperature or in the cold. It is clear enough that there occurs a considerable hypertrophy of this tissue in the cold, and that the nature of the diet has no particular effect on the fresh weight at either temperature.

Table XL shows the changes in the ascorbic acid content of the brown fat with diet and environmental temperature. It is seen that at room temperature the vitamin content is doubled on the high fat ration. In the cold, there is a tremendous rise in the ascorbic acid content, but no difference between the high-fat and low fat groups. This is in line with previous findings of Dugal (20) concerning the liver and kidneys. Actually the vitamin C level in the brown adipose tissue reaches a level as high as that reported by Dugal for livers under comparable conditions.

The only conclusion I wish to draw is that the extreme activity of the brown fat in animals exposed to cold gives at least a hint of the particular importance of fat metabolism in such situations.

Sellers: Dr Pagé, you have shown in the cold, as Forbes (4) did at room temperature, that a high-fat diet is utilized more efficiently than a low fat diet. But what is the evidence that a high-fat diet, at the level you have studied, is utilized more efficiently in the cold than the same high-fat diet at room temperature?

TABLE XXXVIII

Liver and Muscle Glycogen Following Glucose Absorption

	Room Temperature	P		Cold Room	P	
Absorption period (hrs.)	1		3	1		3
Liver Glycogen mg /100 gm liver*	950 ± 95	< 01	1379 ± 168	651 ± 119	< 01	1791 ± 257
mg /100 gm. B.W *	21 0 ± 2 19	< 02	34 1 ± 4 09	18 0 ± 3 32	< 01	52 7 ± 7 63
% glucose absorbed deposited as liver glycogen	2 4		5.2	0 6		7.8
Muscle glycogen* mg/100 gm.	612 ± 42	0 6	649 ± 52	657 ± 19	0.2	742 ± 60

See Tabl XXXVI for corresponding fasting values.

Reprinted, by permission, from Pagé, E and Babineau, L M. Tissue glycogen and glucose absorption in rats adapted to cold. *Canad J Biochem & Physiol* 32, 393 (1954)

TABLE XXXIX

Effect of Diet and Environmental Temperature on the Fresh Weight of the Brown Adipose Tissue

	Number of Rats	Brown Fat (gm.)	Value of "t	Brown Fat per 100 gm. B W	Value of "t
A Room temperature					
Initial control group	10	0.26 ± 0.015		0 09 ± 0 026	
Low fat group	5	0.80 ± 0.03	1 64	0 21 ± 0 01	0 06
High fat group	26	0 91 ± 0 06		0.22 ± 0 01	
B—Cold Room					
Low fat group	24	1 30 ± 0 05	1 96	0 47 ± 0.02	0 90
High fat group	24	1 52 ± 0 10		0 51 ± 0 03	

Values of t exceeding 5.20 are found in all cases when comparing the low or high fat group in the cold with its control group at room temperature.

Reprinted, by permission, from Pagé, E and Babineau, L M The effects of high-fat diets and cold environment on the ascorbic and content of the brow dipose tissue *Canad J R s S ci E 28, 196 (1950)*

TABLE XL

Effect of Diet and Environmental Temperature on the Ascorbic Acid Content of the Brown Adipose Tissue

	Room Temperature	Cold Room	Increase in the Cold (%)	Value of t
A—Ascorbic Acid concentration (γ/gm.)				
Low fat group	65.3 ± 14.8*	305.6 ± 41.1	368	5.50
High fat group	119.4 ± 19.5	353.7 ± 36.9	196	5.62
Increase on high fat ration (%)	83	16		
Value of t (low vs high fat)	2.22	0.89		
B—Ascorbic Acid content (γ)				
Low fat group	52.4 ± 6.4	437.5 ± 64.1	735	5.98
High fat group	103.2 ± 11.4	455.2 ± 62.7	341	5.52
Increase on high fat diet (%)	97	4		
Value of t (low vs high fat)	3.88	0.19		
Standard error $\sqrt{\frac{\Sigma d^2}{n(n-2)}}$				

Reprinted, by permission, from Pagé, E., and Babineau, L. M. The effects of high fat diets and cold environment on the ascorbic acid content of the brown adipose tissue. *Canad J Res Sect E 28, 196 (1950)*

Pagé On the basis of food intake, there is no evidence at all In fact, the efficiency of utilization was the same as at room temperature The only evidence I have as to the superiority of high-fat rations are changes in total body weight.

If rats are kept at room temperature, the ones on the high-fat diet overeat and eventually become larger and fatter In the cold, the animals on the high-fat diet also become larger however it is not deposition of fat as much as it is growth I must say that I am more interested in the fact that finally on either diet, they both seem to utilize fat preferentially

Sellers There is little doubt that there is an optimum level of fat for maximum growth at any temperature However perhaps this can go too high and produce an adverse effect on growth I am inclined to agree that fat metabolism is affected by the process of acclimatization, but my thoughts on it are still rather confused I gather, in spite of the evidence you have presented, that perhaps your thoughts are not entirely clear either on just what the processes are that differ when fat at optimum level is fed in the cold compared to the optimum fed at room temperature.

Pagé I do not know what would be the optimum level in the cold. It would certainly become too high if the protein level were changed at the same time There is the case of exclusive pemmican feeding, a high fat and protein diet with little or no carbohydrate As to my thoughts not being entirely clear they will not be for a long time. It helps however to have a sort of a provisional scheme by which to plan experiment.

If I were to summarize my present views, as of today I would say that the major fuels are burned by way of fat oxidation Why I do not know but if it is so this means that for a given amount of glucose absorbed more of it will be transformed into fat. In other words, there is probably an increased lipogenesis from carbohydrate, and this might account for the larger livers on either a high-carbohydrate or a high-protein diet.

A second point is, what happens to the animal? Does it mean that there are relatively more extrahepatic oxidations, and would that increase the efficiency of heat production? As Dr Horvath suggested, we do not even know whether that fat is oxidized directly or through the production of carbohydrate

Barton In these problems I should like to put in a plea for intermediary metabolism, and for direct calorimetry as well, because of the difficulty Dr Pagé had about the possibility of analyzing metabolism. My thinking has largely been influenced by Weir (21) who analyzed the whole question of carbon dioxide, oxygen, and heat, using the fundamental information in our possession. From the work of the last 60

years in biochemistry which has given us an understanding of the oxygen and carbon dioxide involved when different foodstuffs are burned, and also from the results with the bomb calorimeter we can start off with the equation for oxygen in terms of the amount of fat, carbohydrate and protein that is burned Similarly we have an equation for the carbon dioxide in terms of the amounts of the three different foodstuffs that are burned. The coefficients a b_1 c a_2, b_2, c_2 can be found in Weir s paper

$$O_2 = a\ (F) + b_1\ (CH) + c_1\ Pr$$
$$CO = a_2\ (F) + b\ (CH) + c_2\ Pr$$

These equations are based on the assumption that there is complete balance in oxidation to water and carbon dioxide, and that no interconversion is taking place That is to say there is not an interconversion of fat to carbohydrate or vice versa, at the end of the period As we see, there are three unknowns the fat, carbohydrate, and protein in the metabolism, and only two equations That is not enough to solve the problem, unless we make some assumption about the protein. As we know in the case of humans, we use the nitrogen excreted to estimate the protein burned.

$$N_2 = a\ (Pr)$$

That gives us three equations for working with the three unknowns. We can ascertain how much of each foodstuff is burned in the case of human subjects. I have had no experience, with this but I assume it would be rather difficult to estimate the protein metabolism from urinary and fecal nitrogen in rats, would it not?

Pagé No but every so often we read that protein catabolism is so small over such a short period that it is not worth determining It does not affect the R.Q appreciably

Burton With the three equations, it is possible to know theoretically what has happened in these three foodstuffs, still on the assumption that there has not been interconversion

However there is another equation from the fundamental thermodynamics, that the heat is equal to the sum of some other known coefficients times the carbohydrate, fat, and protein burned

$$H = a\ (F) + b_4\ (CH) + c_4\ (Pr)$$

If we combine direct and indirect calorimetry we have four equations and only three unknowns.

These equations, then, will tell us whether or not the assumption about interconversion is correct. L. A. MacHattie, in my laboratory at the University of Western Ontario has done this. He measures the oxygen, the carbon dioxide, and the calories, although he has not been measuring nitrogen He calculates the calories per liter of carbon dioxide, and the

calories per liter of oxygen, and he makes a sort of a triangular diagram. Each experiment has a given point on the diagram, and from there one can read off the percentage of calories from protein, from fat, and from carbohydrate.

Horvath How can it be done without measuring the protein?

Barton That is on the assumption that there is no interconversion. If there were the point presumably might fall outside this diagram. If the urinary and fecal nitrogen were measured also the presence or absence of interconversion could be checked. The analysis is so complicated that I think we shall never obtain the final answers until we do a great deal more work on it.

The last equation is for the heat, and it is based on the last 60 years work on bomb calorimetry

If we measure the direct heat from the animal, as well as the respiratory exchanges and nitrogen, we ha e four equations and only three unknowns.

P gl Dr Carlson, could you tell us about the amount of activity that would disturb these relationships I wonder if the activity of the rats in the direct calorimetry might not be large enough to upset your calculations.

Horvath One would be measuring the heat directly by calorimeter I think, basically most of these data must be available because certainly some data of the very early work of Lusk (22) and those who followed him, are available

Barton All the coefficients in the four equations are known. I am just pointing out that by having direct calorimetry as well as indirect, it is theoretically possible to solve the whole problem, ignoring all the experimental difficulties, of course

Carlson I wish to call attention to the experimental difficulties which invol e an accuracy of one o two per cent in the direct and indirect calorimetry

Horvath Isn t that the principal reason why most of the direct measurements of heat have been discarded One cannot do much with it in a short period of time one should have at least 24-hour period to work out the nitrogen fraction, and to do a reasonably sound job

Carlson. That would be necessary to obtain the nitrogen fraction, but in the rat, with the calorimeter I think an hour to three hours would be sufficient

Barton There are three unknowns one can use three equations. The oxygen, carbon dioxide, and heat will provide an answer if there are no interconversions The fourth equation is needed to check whether that assumption is correct.

Sellers What about your assumption, Dr Burton, "if there are no interconversions"?

Burton I am pointing out that we can check the assumption if we have the four measurements it can only be done by direct analysis of the carcass sometime later If we do not have all four, we can measure any three of them and make the assumption then we can ascertain how much of each fuel was burned. However the assumption cannot be checked without all four measurements

Crismon I think we have evidence, in a very simple form, that the assumptions are not warranted in the rat. If they are starved for 24 hours, the liver glycogen is found to be at very low levels If the starvation is continued for an additional 24 hours, the liver glycogen is found to be above the level at 24 hours The conversion from the precursor must begin long before it can be detected as a rise in liver glycogen. Accumulation of carbohydrate as liver glycogen represents sufficient glyconeogenesis to provide carbohydrate at a rate in excess of the over all rate of carbohydrate oxidation.

Burton That means that our deductions as to the fuel burned from the oxygen, and carbon dioxide alone, and assuming something about the nitrogen, are quite wrong are they not?

Crismon It means we are merely fortunate in having a number of things going on that ordinarily tend to cancel each other out Some unusual situation may be superimposed, such as placing animals on a low or high fat diet, and subjecting them to cold.

Sellers One of the most interesting things that Dr Pagé reported was the increased rate of absorption of glucose from the intestinal tract. Previously we could guess that more glucose was absorbed because more food was consumed and more heat produced, but we are glad to have it confirmed by the figures

Horvath If I recall correctly the rates of absorption are much lower than at normal temperatures, even in adapted rats? Didn t the absolute rate of absorption of the glucose have a lower value in the cold-adapted rats than in the normal rats at 29 C.?

Pagé Absorption was measured at 29 C. in rats adapted to cold, as well as in the others

Crismon Dr Pagé, I should like to ask about the histological appearance of the brown fat Why is brown fat brown do you know?

Pagé No I do not know I have done no histology on it I wonder if there is a brown pigment that looks the same as the brown pigment Dr Brown found in livers

Crismon Has it any function as an endocrine organ?

Pagé There is some evidence. Hook (23) showed that extracts of the brown fat will lower the basal metabolism of rats

Crismon. Is that the same as the hibernating gland?

Pagé Yes It is very responsive to most hormones (24) If we administer thyroxin, we obtain a large deposition of fat in the brown fat, while the other fatty tissues melt away with increased metabolism. The glycogen goes up in the brown fat, and goes down in the liver Cortisone also causes fat deposition The two together ha e a synergistic effect Epinephrine is the only hormone I have tried which reduces the fat content in the brown fat.

Travell How long does that effect last?

Pagé You mean in animals kept in cold, or removed from the cold?

Travell After they are removed from the cold.

Pagé Dr Sellers could answer that

Sellers I cannot answer it except by guessing from the other related data I think it might pass off rather quickly perhaps within a week, or possibly less

Behnke Why is the growth retarded in cold?

Pagé I have no idea. I was interested in the fact that when the animals took a long time to recover their initial weight, they seemed to do far better than those that resumed their initial weight more quickly There are only two sets of data, of course, which are not enough for generalizations. If we have an increase in heat production in the cold, we might say that we have a mechanism that is quite different from the metabolic stimulus of growth.

Behnke In the rats, what was the relative percentage of fat at room temperature and in the cold?

P gé On a body weight basis?

Behnke Yes.

Pagé At room temperature the fat content was 87 gm on the high-fat ration, and 58 gm. on the low fat ration. In the cold it was 29 and 33 gm. respectively but the animals were smaller As regards per cent of body weight, it was 15 and 20 per cent at room temperature, and 10 and 11 in the cold, respectively The rats were nearly twice as fat at room temperature.

Barch Was reproduction the same in the cold as at room temperature

P gé I could not tell you.

Barch Were maturing and aging influenced in the rats?

P gé I do not know

Barch There may be smaller animals that go through the normal growth.

Horvath If they follow McCay's work (25) they ought to live longer

Carlson Why should they live longer?

Horvath He put his animals on low-caloric intake so growth was retarded, and they lived for a much longer period of time.

Burch By growth, do you mean total body mass?

Horvath Yes.

Burch Could they still be growing maturing, and aging that is, going through the life span, in an essentially normal fashion?

Horvath They were not going through it in the normal fashion, but in a retarded fashion.

Burch I mean in terms of having the same number of total cells in the body

Horvath I think so At least they lived a lot longer in terms of days, by 20 per cent and by 30 per cent in some cases, depending on the level of growth retardation.

Burch Were the turnover chemical phenomena even greater?

Sellers I think probably Dr Dugal could comment on longevity and morbidity in the cold. In our own experience, the mortality at all periods in the cold was higher than in our usual rat colony I do not have precise figures on that, but on the basis of work over the last five years I am fairly sure that is the case.

Stevenson I would agree, but I think we have to be careful about what seem like small differences in temperature In terms of morbidity and mortality there may be great differences in the range between 10 and 1 C. We are then approaching the range where we may observe peripheral damage occasionally That might make all the difference. It may be as important as the presence or absence of metabolic adjustment.

Burch Why did the animals die?

Sellers Within the first week or so of exposure, I think the commonest cause was hypothermia. Also within the first couple of weeks, a very common cause, with rats anyway was that they tended to bite their tails and lose a fair bit of blood. I suspect that the loss of blood, superimposed on the stress of the cold, was enough to lower their resistance and result in death. However after the first couple of weeks, findings of death from hypothermia, or associated with hemorrhage, were not common. I think probably the incidence of infection, was higher than in rats kept at room temperature, but beyond saying that rats dying at this stage often had pneumonia, I cannot give you any definite figures.

You asked about the effect of cold on fertility We have often bred animals in the cold, and again I cannot give you a numerical statement on fertility but I can say that between 1 to 2 C, Wistar strain rats,

both male and female, remain fertile for at least a year-and a-half of exposure to that temperature. However I have never seen them successfully rear their offspring at that temperature, because we do not give nesting material to the animals we think it affects the development and degree of acclimatization. In every case that I can remember the young rats have not lasted longer than three or four days.

Birch Was the litter the same size, and was the size of the offspring at birth as large?

Sellers They appeared to be, Dr Burch, but all of these latter remarks are incidental findings, and are impressions rather than mathematically expressed results.

Behnke In the rat experiments, were you working at a temperature that does not produce peripheral injury?

Pagé At between 1 and 3 C there is injury At such near freezing temperatures, there is occasionally a frostbitten tail and gangrene If it is bad enough, the rats will bleed to death

Carlson In rats that were 60 days old, at 5 C, we almost always observed pathology of the kidney

Dugal I was going to say that we had nephrosis, especially in the male, and most of the time we observed edema of the penis, at least during long exposures to cold (26)

Carlson. We have seen that In the rat, we have also observed an increased output of urine, that continued during the time they were in the cold.

Stevenson That is interesting because, in our experience, they have a much-reduced water intake, certainly relative to the amount of food they eat.

Carlson. In the data we had, the urine output was so great that we examined every possibility of inaccuracy in our collection methods

Stevenson. Did you measure the water intake?

Carlson Yes

Stevenson. Was that also increased, relative to the increase in food intake?

Carlson Yes.

Stevenson What happened to the other avenues of loss? Was the rat losing much less by extrarenal paths, and if so which ones?

Carlson. As I say we felt that our data required explanation before they were published.

Horvath Fat is preferentially oxidized. If much water were obtained from oxidation, one would have a slight increase in water With greater consumption of fat, there should be more water available for urine excretion.

and to cold they have practically no fat, in contrast to the Eskimos. Have any experiments been done on rats in which two stresses were operating low-oxygen tension and cold?

Blair Dr M. J Fregly (27 28) did just that. He placed the rats in the cold at low atmospheric pressures over a long period of time to study the combination of low-oxygen pressure and cold on the rats.

Burton They withstood the low oxygen better when in the cold than when they were placed in the warm?

Blair I think that is correct, Dr Burton.

Dugal Captain Behnke, you were asking what retards the growth of rats in the cold. I have no complete answer but we made a recent experiment with growth hormone and we can prevent that situation. The growth can be normal in the cold for rats of 60 gm., if they are injected daily with 4 mg of STH In that case we obtain the same growth curve as at room temperature

Horvath You mean you retard the pituitary excretion of growth hormone when they are placed in the cold?

Dugal No I did not say that.

Horvath It seems to me that would be the implication.

Stevenson These were short-term experiments, lasting three weeks, at from 3 to 5 C. When we offered rats diets that were high in protein, fat, or carbohydrate, but made isocaloric with celluflour the caloric intake was approximately the same on all three diets. The high-protein-fed rats, however did not maintain their weight Although they were losing the most weight, they would not increase their caloric intake. Food was available *ad libitum* but these animals did not make use of it, in spite of the weight loss.

Pagé Dr Dugal, would you say it was beneficial to the rats to maintain weight gains similar to rats at room temperature through excess growth stimuli?

Dugal I do not know We tried less than 4 mg of STH, and it did not prevent the loss of weight, but with 4 mg it did. Ershoff (29) tried 1 5 mg but did not observe any effect in the cold.

Behnke What is the temperature at which rats begin to lose weight, or at least fail to grow in a normal manner?

Pagé The only guess I would dare make is 14 C., for rats of about 110 gm. however they happened to grow as well as at room temperature in the one case that was studied. I am working at higher temperatures because I feel the animals adapt more quickly and one avoids an unnecessary stress.

Behnke Someone has worked with rats at 10 C., have they not?

Pagé Yes.

Horvath Did that retard them?

Pagé The growth curve was not as good as at room temperature.

Dugal The peculiar thing is that a rat of 200 gm may lose weight at 5 C. for about a week, and a rat of 60 gm. will lose weight at 2 C. for only one day

Blair What criteria are we to use? If we take a growing rat and put it in the cold, it does lose as great a percentage of weight as a fully matured rat placed in the cold. If we take, say a 150 gm. rat that is growing and put it in the cold, the per cent loss of body weight in the same exposure period is not as great as with a 350 or 400 gm. rat under identical conditions.

Pagé I think I mentioned earlier that the younger rat has a larger growth stimulus and cannot curb it as easily as an older rat. There may be some antagonistic mechanisms

Blair The other rat is grown and probably has no growth stimulus.

Stevenson The young rat seems to have the drive to take in calories, in order to grow as well as to keep warm. The older rat apparently does not it is apparently satisfied on a high-protein diet, with a food intake level not adequate to maintain weight.

Blair The older rat does increase the caloric intake in the cold quite markedly but possibly not as much as the growing rat

Stevenson. What I mean is that the rat on the high-protein diet will increase its caloric intake in the cold only as much as the rat on a high-carbohydrate diet, although at this equal caloric intake it is not maintaining weight nearly as well as the one on the high-carbohydrate diet. I wonder why it does not eat more

Pagé It could, if it wanted to

Carlson. I should like to return to the idea about the change that takes place in the cold, which I gather is essentially that the animal appears to metabolize fats at higher rate Is that correct, Dr. Pagé?

Pagé It would seem so but if I knew why I would be more certain.

Carlson I was wondering if this is not open to an experimental approach Whether it is converted to glycogen, or oxidized, it goes through the same common point in two-carbon fragment It seems to me we know a lot about the pathway of this change now and we should, perhaps, look for the ability of the liver to convert.

Pagé It would be very profitable, obviously to do that

Crismon What would one look for active acetate, or coenzyme A activity?

Carlson First of all, in labeling experiments one could determine the derivation of the oxidized products, and analyze the glycogen for

radioactive carbon. Coenzyme A seems to be involved in this transition. I have always thought of the two-carbon pool as being a critical point in the metabolic cycle, because as the animal needs energy it can draw from protein, fat, or carbohydrate, and each energy source except *glutamic acid goes through* this common point. (Glutamic acid enters the Krebs cycle elsewhere) Eventually there is a change in the enzymes required to mobilize energy

I like to think of the endocrines in this respect too because during the period of transition, perhaps these hormones are necessary Once the enzymes have been altered in such a fashion as to be adequate for the increased metabolism, then the endocrine response is not required.

Coffey Colonel Blair would you tell us a little more about the Fort Churchill experiment you mentioned?

Blair Yes. We brought a group of seven test subjects from Fort Knox, Kentucky who stayed at Fort Churchill for a three-month period, living and working in heated barracks, and eating camp rations in the mess halls. They gained weight, but they received very little stress to cold. However when these subjects were taken out on a 15-day bivouac, living outside in pyramidal tents with little or no heat, and doing a controlled amount of marching daily they lost weight During that same period they were on C field rations, which may not have been as agreeable and appetizing as the mess ration.

But the point I wish to make is this just because a person goes to the North and gains weight is no indication that he has gone into the cold and gained weight If he goes into stressing cold, it may very well be that he will lose weight as these animals have.

Horvath There were a combination of stresses in the experiment Colonel Blair cited If a man is given a fixed diet and a certain amount of activity in a warm environment, and is then shifted over into a cold environment, he does not lose weight if he has adequate calories This has been done giving 3 600 calories beforehand, and the same amount in the cold.

Blair Eskimos and many trappers have a fat appearance, and do not lose weight, like Dr Pagé s animals, while living and working in the far North. They are not forced to take in any amount of nutrition, but voluntarily consume as many calories as they desire. However if these men were put under the same conditions to which Dr Pagé subjected his animals, it is quite likely that they would follow the same pattern and lose weight also

Behnke Arctic animals, both land and aquatic, are usually fat, even excessively fat. The implication is that existence and survival in the cold depend upon a high fat content of the body But in the laboratory

the animals subjected to the cold environment are not limited to those with a high-fat content.

Blair The caribou is a very lean animal

Horvath He is fatter at the beginning of winter and becomes leaner towards the end.

Blair Exposure to the cold causes a decrease in weight

Carlson. That is what happens to the rat.

Horvath. There is a lack of available food supply in the case of the caribou that is a different problem. During the first part of the winter when it has enough food from a storage supply it does not lose weight.

Blair Another point is this in aquatic animals, like the seal and walrus, a change from a warm to a cold environment is actually relatively slight. Water temperatures in the Arctic do not vary nearly so much as the 30 to 50 C. drop that these experimental animals are subjected to What happens to these rats, as Dr Pagé said is that they are given such a severe cold stress that they can only survive but cannot maintain their growth of body fat Humans, if put under a similar degree of cold stress, may follow the same pattern of response.

If the animals die, I think the explanation of chewing the tail seems rather poor You mention the kidney To what extent have histological studies been made of rats exposed to cold?

Carlson I cannot quote them, but there are some in the literature (30 31)

Sellers. Most of these reports differ in essential particulars. There is no doubt that rats occasionally develop pyelonephritis, and also hydronephrosis, probably secondarily to the balanitis which is commonly seen. This is not a true balanitis, but something resembling that condition which occurs in male rats in the cold It accounts for the death of some of them

In cases of immersion foot that is produced experimentally in rats, it has been described as a tubular degeneration, or lower nephron nephritis, which develops. I have observed this and the histological appearance is somewhat different from that usually seen in other experimental renal lesions in that it is very spotty By that I mean a tubule, or group of tubules, in one part of the kidney will show extensive degenerative changes then there will be an area that appears to be quite normal and next to it other tubules will show the degenerative change. This condition does not occur consistently in the animals that are subjected to our experimental conditions.

Whether immersion foot is produced in animals in which kidney lesions are common, and represents an additional factor which precipitates the disease, I do not like to say In long-term experiments of from

12 to 18 months, we found an interesting glomerular change there was a deposition of fat, either in the capillaries of the glomerulus, or between the capillary wall and the endothelial lining of the glomerular capsule. It did not appear to be an extensive enough lesion to account for death. It is not easily seen under H & E staining There are also fatty degenerative changes in the tubular cells, and dilated tubules containing casts. Nevertheless on the whole I should say that the kidneys of animals which have been in the cold a long time are remarkably normal in appearance. Incidentally there are no vascular changes there that I have been able to detect.

Coffey You mentioned a sex difference. In rat mortality is the male more prone than the female?

Sellers I think the reason more of the males develop pyelonephritis and hydronephrosis is because the urine is improperly eliminated due to inflammation in the penis

We have spent considerable effort in trying to demonstrate a sex difference in mortality and I am still not certain of what the results will be There is some indication that the females have a greater resistance to cold but I am not convinced that our figures cannot be explained on some other basis It cannot be a very remarkable difference, or it would have been more clearly indicated by the number of studies we have carried out. Perhaps some of the others who have done this sort of work can answer the question.

Horvath What is the longest period of time that an animal has been kept at any specific temperature?

Sellers About two years

Horvath At what age did these animals start the experiment?

Sellers They started at an approximate weight of from 170 to 180 grams

Horvath Would they be about 100 days old then?

Sellers Yes

Horvath So they almost lived out their life span, which is roughly from two to two-and-one half years, under the experimental conditions.

Blair We used all male rats in a weight range of from 350 to 450 grams They were exposed 16 hours each day for 50 days, at −5 C, and they were out of the cold room for eight hours per day for observation, watering, and feeding We lost about ten per cent of the total, almost all of them during the first week of cold-acclimatization.

Rabbits were exposed 20 hours each day for 50 days, at −5 C, with four hours out of the cold for observation, watering, and feeding All animals were acclimatized to cold over an arbitrary 50-day period.

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DIET AND SURVIVAL

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WE HAVE BEEN INTERESTED in the responses of the body to nutritional and environmental stresses and in the effect of previous diet on these responses. The studies I am about to describe have been supported by our hosts, the Defence Research Board of Canada. They are, in most instances, not yet complete, but we have tried to abstract those parts pertinent to this conference's interests in cold physiology I have been assisted by Mr R. H Rixon, who has done a considerable amount of the work that we shall review and also by Miss L. R. Miyata and Mrs R Smith, all members of the Department of Physiology University of Western Ontario

As you remember in 1938 Mirski, *et al* (1) reported that the liver glycogen was better maintained in early starvation, that is, during the first 24 hours, following a high-protein diet than after a high-carbohydrate or high-fat diet. This difference disappeared as starvation continued. This protein effect was absent in adrenalectomized rats, and these workers attributed it to the enhanced gluconeogenesis already stimulated by the high-protein diet Samuels and his group (2 3 4, 5 6, 7 8) did considerable work on this in the 1940's, and concluded from studies using eviscerated and nephrectomized animals as well as intact rats, that liver glycogen is better maintained in early starvation following a high-fat diet because the peripheral tissues are accustomed to metabolizing fat They believe this also occurs after a high-protein diet because of the already increased gluconeogenesis. They found the longest survival during starvation among the previously fat fed animals, and the shortest in the protein-fed animals. They used forced feeding, and diets containing only fat or only carbohydrate in addition to protein in many of their studies, procedures which themselves may have specific effects upon metabolism.

We have carried out somewhat similar investigations on rats in both temperate and cold environments, but have restricted the exaggeration of the diets to within more likely limits The three isocaloric diets which have been regularly employed are as follows

High-carbohydrate diet.

CHO 70 per cent casein 20 per cent, fat 10 per cent (HCD)

High protein diet

CHO 20 per cent casein 70 per cent, fat 10 per cent (HPD)

High fat diet

CHO 10 per cent casein 20 per cent, fat 70 per cent (HFD)

The approximate composition of these diets is expressed as the percentage of total calories contributed by each foodstuff As you will observe each diet contains some of all three major foodstuffs. The diets are made isocaloric (4 2 calories per gm) by the addition of celluflour All the known mineral requirements have been included in the salt mixture at 4 per cent of the diet by weight. Generous amounts of fat and water soluble vitamins have also been added on an isocaloric basis Water has been available at all times Sprague-Dawley rats have been used and have been fed fox chow prior to the actual experiment. Constant environmental temperatures of 22 to 23 C. (72 to 74 F temperate) and 2 to 5 C. (36° to 40 F., cold) have been employed

In the first experiment that I shall mention, rats weighing about 300 gm. were fed one of the three diets in the temperate or cold environments for a period of three weeks, during which food and water intakes were measured. They were then sacrificed in the fed state, or after 24 or 45 hours of food starvation The groups sacrificed in the fed state, or after 24 hours of starvation consisted of ten rats each. The groups sacrificed after 45 hours of starvation consisted of 20 rats each.

All dietary groups consumed approximately 25 calories per 100 gm of body weight per day in the temperate environment, and about 40 per cent more in the cold. Despite equal caloric and protein intakes the water consumption was always greater by 10 to 20 per cent on the high-fat diet than on the high-carbohydrate diet This may have been caused by the ketonuria resulting from the high-fat diet. The high-protein diet, of course, caused a very much greater water intake, i.e., 75 to 100 per cent.

Representative weight gains for the three weeks on the experimental diets are shown in Table XLI. Weight gain was least on the high-protein diet, and in the cold the greatest weight loss occurred on this diet. Despite this lack of weight gain, or normal growth, the animals on the high-protein diet continued to show caloric intakes almost identical with those on the high-carbohydrate and high fat diets In this instance the food intake was more closely correlated with caloric content than with the maintenance of growth

In Figure 22 are shown the body-weight loss during starvation periods, and the blood sugar liver glycogen and muscle glycogen at

TABLE XLI

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Diet	Number of Rats	Temperate Environment (22 C.)	Cold Environment (from 2 to 5 C.)
HCD	40	+ 52.35 gm	+ 3.98 gm.
HFD	40	+ 58.87 gm.	+ 1.70 gm.
HPD	40	+ 40.13 gm.	− 21.28 gm.

autopsy In these figures, each group of three columns represents the fed, 24-hour fasted, and 45-hour fasted states, reading from left to right on a particular experimental diet The dietary groups are indicated by

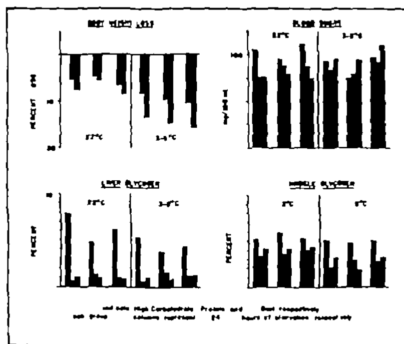


FIGURE 22. Effect of previous diet on the responses during early starvation in temperate and cold environments.

a) High-carbohydrate diet
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b) High-protein diet:
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The approximate composition of these diets is expressed as the percentage of total calories contributed by each foodstuff. As you will observe, each diet contains some of all three major foodstuffs. The diets are made isocaloric (4.2 calories per gm.) by the addition of cellulose. All the known mineral requirements have been included in the salt mixture at 4 per cent of the diet by weight. Generous amounts of fat and water soluble vitamins have also been added on an isocaloric basis. Water has been available at all times. Sprague Dawley rats have been used, and have been fed fox chow prior to the actual experiment. Constant environmental temperatures of 22 to 23 C. (72 to 74° F. temperate) and 2 to 5 C. (36 to 40 F., cold) have been employed.

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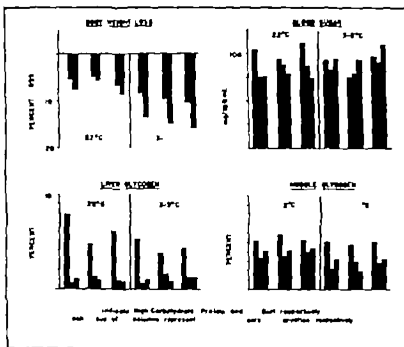


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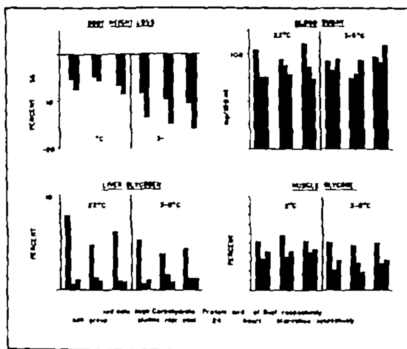


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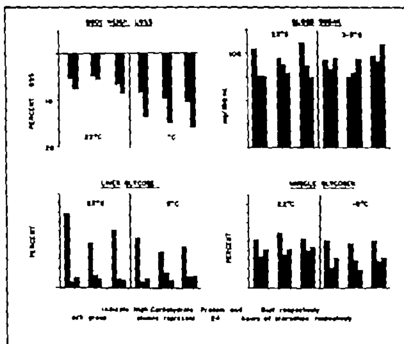


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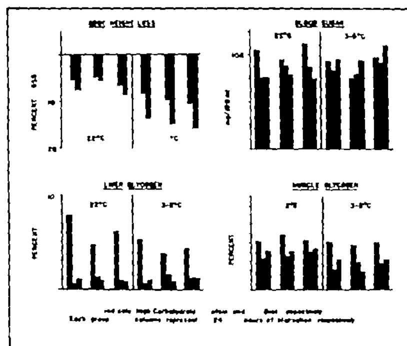


FIGURE 22. Effect of previous diet on the responses during early starvation in temperate and cold env ronments.

the capital letters above or below the groups "C" indicating the high-carbohydrate diet, "P" the high-protein diet, and "F" the high-fat diet. The results in the temperate environment appear to the left, and those in the cold environment to the right in each figure.

As you can see, the body weight loss was greater in the first 24 hours than in the second 24 hours following all diets: of course, it was proportionally much greater in the cold. The average cumulative loss of body weight after 24 hours of starvation was about 5 per cent, and after 45 hours 7.5 per cent, in the temperate environment. In the cold it was about 9 per cent after 24 hours, and about 14.5 per cent after 45 hours. The HFD rats seemed to gain a little better than the others in the cold. This was not very pronounced, but they were usually a little bit ahead of the carbohydrate fed animals. On fasting, however, they always showed the greatest body weight loss. That is, they gained more quickly but their weight loss was more rapid also.

Although sacrifice by decapitation may impair the accuracy of muscle glycogen determinations, the results are included since they are fairly consistent. In the fed state, previous diet and environmental temperature seemed to have had little specific effect. Starvation reduced the level of all groups slightly at 24 hours but no further drop occurred at 45 hours of starvation. The decrease was somewhat greater in the cold at these times, perhaps due to increased muscle activity. In the blood sugars, although none of the differences was very great, in the fed state on all diets the blood sugar was lower in the cold than in the temperate environment, whereas in the starved state the opposite was true. In the fed state, both in the temperate and cold environments, the highest blood sugar appeared on the high fat diet. This was also the case in the cold following 24 or 45 hours of starvation.

In Figure 23 you will see that in the cold, even in starvation, the livers were slightly but consistently larger relatively; this was also true for absolute weight. In starvation the liver showed a marked decrease in weight during the first 24 hours, but little further decrease at 45 hours. In the fed state, both in temperate and in cold environments, the order of liver size was always HCD > HPD > HFD. Upon starvation, however, this hierarchy was obliterated and no particular correlation appeared. The organ weights have been expressed as a percentage of body weight because of the great variation in the latter with starvation. The kidneys were always larger, absolutely and relatively, in the cold, probably an effect of the increased food (protein) intake in this situation, for in any nutritional and environmental state the HPD group showed the largest kidneys. In starvation the kidney showed weight loss more or less proportionate to the body loss as a whole.

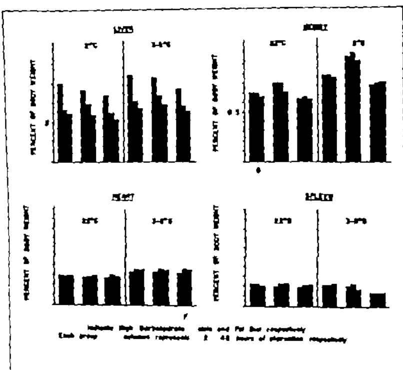


FIGURE 23. Effect of previous diet on the responses during early starvation in temperate and cold environments

The cold produced an increase in heart weight on all diets, about 5 per cent on an absolute, and somewhat more on a relative, weight basis. *Is this only an indication of protection of the heart under adverse conditions*, or is it evidence of cardiac hypertrophy in response to increased work in the cold? On acute starvation in the cold the heart showed only slightly less weight loss than the body as a whole. In general, diet and environmental temperature had little effect on the absolute or relative weight of the spleen. In starvation, weight loss of this organ was proportionate to that of the body generally.

As shown in Figure 24, the cold environment caused an increase in adrenal weight of about 25 per cent on all diets and this was enhanced, relative to body weight, during starvation, particularly at 24 hours. In any given condition of starvation and environment the animals on a high-protein diet always showed the largest adrenals. The effect of a high-protein diet on adrenal size has been under discussion for years, but

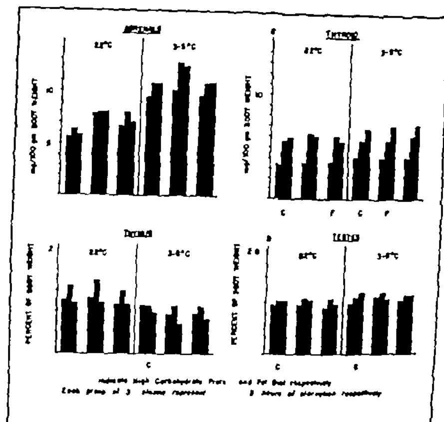


FIGURE 24 Effect of previous diet on the responses during early starvation in temperate and cold environments

it is interesting to note that in this study not even the marked effect of cold obliterated this small dietary influence. No dietary effect on the typical thyroid hypertrophy in a cold environment appeared. This gland showed a protection or hypertrophy of some kind on starvation in both temperate and cold environments Its relative weight increased quite markedly With regard to the reproductive organs, you observe that the testes maintained about the same relation to body weight regardless of environmental temperature or acute starvation.

The changes in liver glycogen, about which there has been some discussion already are shown in Figure 25 The glycogen values are expressed as per cent of liver wet weight. In the fed state in both the temperate and cold environments the concentration of glycogen in the liver was in the order of HCD > HFD > HPD in the cold all were proportionately lower The rate of fall during the first 24 hours of

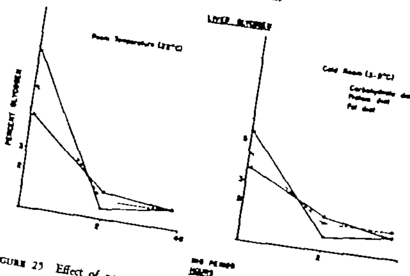


FIGURE 25 Effect of previous diet on liver glycogen during early starvation.

starvation was in the same order the relationship being completely reversed. Although starting from different levels, all dietary groups reached a low level after 24 hours of starvation (about 1 per cent) the HPD providing the highest, and the HCD the lowest, levels in both environments At 45 hours these levels showed little further change the HCD perhaps recovering slightly and the HFD providing the highest (but not by much) level in the cold. These small differences observed in starvation may not reflect important effects on carbohydrate stores as a result of diet, but they may be important as reflections of differences in endocrine and metabolic adjustments The slightly but significantly higher levels in the HPD groups after 24 hours of starvation probably resulted from a previous development in the fed state of a high rate of gluconeogenesis In the HFD groups the previous diet probably enhanced the peripheral utilization of fat, reducing the demands for sugar In the HCD groups the peripheral demand for sugar had not been reduced by the previous diet, nor had there been any previous emphasis on gluconeogenesis these adaptive mechanisms had to be developed after the onset of starvation.

Sellers Are those differences at 24 hours statistically significant?

Stevenson At room temperature yes In the cold the difference between the HFD and HPD groups is not.

Page Were your animals bled to death?

Stevenson No the liver was removed within 30 seconds.

Pagé We usually bleed the rats to death before weighing organs. We find that if the animal accidentally dies under anesthesia and does not bleed profusely that we have quite large differences in liver weights.

Stevenson. These animals were killed by decapitation. The piece of liver for glycogen analysis was removed as quickly as possible without waiting for the animal to bleed, because seconds there make a considerable difference. The rest of the organs were removed after the animal had bled.

Crismon The time between zero and 24 hours is of some interest. In preparing rats for hypothermia studies by starvation, we found the same sort of change occurring on an ordinary stock diet, and became curious about the point at which the lowest glycogen was reached. It antedates 24 hours

Stevenson What size were the rats?

Crismon. They weighed 250 to 300 grams

Stevenson From pilot experiments not adequate for statistical purposes at all our impression is that the smaller the rat (and a difference of 50 gm. would be important) the faster this change in liver glycogen takes place

Sellers Do you think that is the lowest point reached in your experiments?

Stevenson I do not know

Barcb Was there some hypertrophy of the liver?

Stevenson. Yes

Barcb Suppose you expressed it in total grams of glycogen, was there any difference between the two livers?

Stevenson We have not done that as yet, but certainly intend to. These results are shown in Table XLII The relations between dietary groups are the same as when the glycogen is expressed in terms of concentration however the differences in the cold environment are not significant, at least for groups of the size used

As I mentioned, in the cold we have exactly the same relations but at a much lower level. Here the carbohydrate diet provides liver glycogen only a little above 5 per cent, the fat diet a little above 4 per cent, and the protein diet a little below 3 per cent.

The differences seen on starvation in the cold are statistically significant for the HPD and HFD groups compared with the HCD group after 24 hours, but not after 48 hours of starvation. The conclusion we have drawn is that after the first 48 hours or so of starvation it does not really make much difference what diet the organism has been on, in so far as these aspects are concerned

TABLE XLII

Effects of Previous Diet on Glycogen Content of Liver in Early Starvation.

	Hours of Starvation		
	0	24	45
	Temperate Environment		
Diet			
HCD	1 30 ± 0 210*	0 05 ± 0 006	0.08 ± 0.006
HFD	0.80 ± 0 075	0 08 ± 0 009	0 07 ± 0 005
HPD	0 72 ± 0 104	0 13 ± 0 016	0.07 ± 0 008
	Cold Environment		
HCD	0 84 ± 0 123	0 06 ± 0 011	0 08 ± 0 013
HFD	0 55 ± 0 071	0 11 ± 0 017	0 10 ± 0.011
HPD	0 53 ± 0 163	0 18 ± 0 070	0 08 ± 0.021

* Mean (± S E M.) glycogen content expressed as gm per whole liver.

Another study which I thought might be of interest was one concerning dietary influences on duration of survival. Rats which had been fed one of the three isocaloric diets for three weeks in the temperate or cold environments were submitted to continuing starvation in the same environment. Water was available *ad libitum* throughout. The results are shown in Tables XLIII and XLIV No appreciable difference in duration of survival or proportion of body weight loss at death was apparent between the various dietary groups Survival in the cold was of course *much shorter and the proportion of body weight loss at death was less*, as seen in Table XLIV The tables show the body weight before the fast, the erage number of days survived, and the percentage of starting body weight lost from the beginning of the fast until death A group previously fed ordinary laboratory fox chow is also included. There seems to be little difference between the HCD HFD and HPD in the effect on the duration of survival in complete starvation. You will notice that these animals previously consumed almost exactly the same amount of food per day i.e., 21 grams. Here again, the high-protein diet animals took about the same number of calories as the animals on the other diets, despite the fact that they did not gain weight nearly as well.

The effect of restricted amounts of food, survival rations, on the duration of survival is also shown in Tables XLIII and XLIV The

Stevenson No the liver was removed within 30 seconds.

Pagé We usually bleed the rats to death before weighing organs. We find that if the animal accidentally dies under anesthesia and does not bleed profusely that we have quite large differences in liver weights.

Stevenson These animals were killed by decapitation. The piece of liver for glycogen analysis was removed as quickly as possible without waiting for the animal to bleed, because seconds there make a consider able difference. The rest of the organs were removed after the animal had bled

Crismon The time between zero and 24 hours is of some interest. In preparing rats for hypothermia studies by starvation, we found the same sort of change occurring on an ordinary stock diet, and became curious about the point at which the lowest glycogen was reached. It antedates 24 hours

Stevenson What size were the rats?

Crismon. They weighed 250 to 300 grams.

Stevenson From pilot experiments not adequate for statistical pur poses at all, our impression is that the smaller the rat (and a difference of 50 gm. would be important) the faster this change in liver glycogen takes place.

Sellers Do you think that is the lowest point reached in your experi ments?

Stevenson I do not know

Burch Was there some hypertrophy of the liver?

Stevenson. Yes

Burch Suppose you expressed it in total grams of glycogen, was there any difference between the two livers?

Stevenson We have not done that as yet, but certainly intend to. These results are shown in Table XLII The relations between dietary groups are the same as when the glycogen is expressed in terms of con- centration however the differences in the cold environment are not significant, at least for groups of the size used.

As I mentioned, in the cold we have exactly the same relations but at a much lower level. Here the carbohydrate diet provides liver glycogen only a little above 5 per cent, the fat diet a little above 4 per cent, and the protein diet a little below 3 per cent.

The differences seen on starvation in the cold are statistically signifi cant for the HPD and HFD groups compared with the HCD group after 24 hours, but not after 48 hours of starvation. The conclusion we have drawn is that after the first 48 hours or so of starvation it does not really make much difference what diet the organism has been on, in so far as these aspects are concerned.

TABLE XLIV
Restricted Food Supply and Surv val (Cold environment 2 to 5 C.)

Treatment	Number of Rats	Body Weight (pre fast or restriction)	Survival (days)	Body Weight (per cent loss)	Food Intake Before (gm.)	Food Intake During starvation or restriction (gm.)
Complet starvation						
Chow before	5	285	2	31	40	
HCD "	5	328	3	25	32	
HFD "	5	334	3	26	30	
HPD "	5	317	3	6	29	
Mean			3	27		
Restricted food						
3 5 gm HCD	5	332	4	25		3 5
HFD	5	3 0	3	22		3 5
HPD	5	330	4	26		3 5
Sugar	5	331	4	6		3 5
Mean			4	25		
7 0 gm HCD	5	330	5	33		7.0
HFD	5	332	5	35		7 0
HPD	5	329	5	33		7 0
Sugar	5	326	4	32		7.0
Mean			5	33		

TABLE XLIII

Restricted Food Supply and Survival (Temperate environment 22 C.)

Treatment	Number of Rats	Body Weight (pre fast or restriction)	Survival (days)	Body Weight (per cent loss)	Food Intake: Before (gm.)	Food Intake: During starvation or restriction (gm.)
Complete starvation						
Chow before	5	348	8	37	26	
HCD	5	388	11	41	21	
HFD	5	379	11	37	21	
HPD	5	3 0	10	42	21	
Mean			10	39		
Restricted food						
3.5 gm HCD	5	330	13	40		3 5
HFD	5	329	14	41		3 5
HPD	5	330	15	43		3 5
Sugar	5	330	13	40		3 5
Mean			14	41		
7 0 gm HCD	5	335	29	52		7 0
HFD	5	333	25	49		7 0
HPD	5	328	40	51		7 0
Sugar	5	325	36	54		7 0
Mean			33	52		

TABLE XLIV

Restricted Food Supply and Survival (Cold environment 2 to 5 C.)

Treatment	Number of Rats	Body Weight (pre-fast or restriction)	Survival (days)	Body Weight (per cent loss)	Food Intake Before (gm.)	Food Intake During starvation or restriction (gm.)
Complete starvation						
Chow before	5	285	2	31	40	
HCD "	5	378	3	25	32	
HFD "	5	334	3	26	30	
HPD "	5	317	3	26	29	
Mean			3	27		
Restricted food						
3.5 gm HCD	5	332	4	25		3 5
HFD	5	330	3	22		3 5
HPD	5	330	4	26		3 5
Sugar	5	331	4	26		3 5
Mean			4	25		
7.0 gm HCD	5	330	5	33		7.0
HFD	5	332	5	35		7 0
HPD	5	329	5	33		7 0
Sugar	5	326	4	32		7 0
Mean			5	33		

animals were fed 15 calories (3.5 gm.) or 30 calories (7.0 gm.) per day of one of the three isocaloric diets until death.

There were no marked differences in survival between the dietary groups at the same intake level, except for the longer survival shown by the HPD group on 30 calories per day in the temperate environment. However the provision of some food, regardless of its source, did increase the duration of survival. On 15 calories per day the average survival was 14 days as against 10 days in complete starvation, and there is some evidence that even this restricted intake permits the animal to metabolize more of its own tissues as a source of energy for survival.

Thirty calories are approximately the calculated daily basal requirement of a rat of 300 gm. as determined by the Brody formula ($Q = 70.5 M^{0.734}$; Q=basal metabolism in calories, and M=body weight in kg.). On the other hand, if one takes 90 or so calories, the *ad libitum* intake of these rats, as the equivalent of 2,400 calories intake for a sedentary man (these are more or less sedentary rats because they live in small individual cages) and reduces them proportionately, then the equivalent of 400 calories for a man would be about 15 calories per day for the rat, or 3.5 gm. of one of these isocaloric diets.

When we fed the 7 gm. diet, the so-called basal requirement by Brody's formula, or in terms of the proportions I just mentioned equivalent to 800 calories for man, we found that the increases in survival times were much more than double those on the 3.5 gm. diet. With the latter there was an average increase of about 40 per cent in duration of survival over complete starvation, but with 7 gm. there was an average increase of from 200 to 300 per cent. The proportion of body weight lost at death was also greater, indicating that the larger ration had also permitted a greater use of body tissue.

In the cold the beneficial effects of these small amounts of food were practically obliterated. Here the total requirement was so much greater as demonstrated by the *ad libitum* intakes which are about 50 per cent greater than in the temperate environment. So the 3.5 and 7 gm. moieties provided proportionately very much less, and did not increase survival to any great extent: three days on straight starvation, four days on 3.5 gm. per day, and five days on 7 gm. per day. In cold environments, temperate survival rations would be quite inadequate unless body insulation were increased proportionately.

In Table XLV are shown the organ weights of these animals obtained at autopsy expressed as percentage of body weight. The only finding to remark on is that in the cold, on the restricted food, the livers were very much heavier relatively and absolutely than they were at room temperature. The hearts were also larger proportionately but the kidneys and

TABLE XLV
Effect of Restricted Daily Food Supply on Organ Weight Relative to Body Weight at Death

	Temperate			Cold		
Food intake (gm per day)	0	3 5	7 0	0	3 5	7 0
Heart (gm per 100 gm. B W)	0 30	0 35	0 34	0 40	0 42	0 39
Liver "	1 67	1 73	2 26	3 09	3 56	2.79
Kidney "	0.85	0 87	0 97	1 00	0 93	0.89
Adrenals (mg per 100 gm B W)	13.2	13 0	12.9	13.8	13 1	13 9

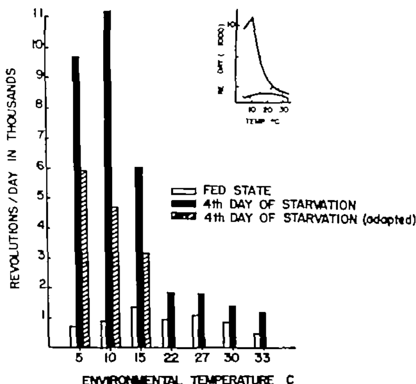


FIGURE 26 Spontaneous running activity f rats on the fourth day of starvation at arious environmental temperatures The adapted animals regained body weight at low temperature before being exposed to the next lower temperature the others regained body weight at 22 C between experiments.

adrenals showed the same relationship to body weight at both temperatures

Turning to a different aspect of the problem, Figure 26 demonstrates the spontaneous activity of the rat when deprived of food. In 1944, Wald and Jackson (9) reported that rats increased their spontaneous activity when deprived of food and water They considered this increased activity to be representative of aimless, persistent wandering, which is the basis of mammalian emigration Another hypothesis to explain this increased activity upon starvation relates both food intake and work output to the maintenance of body temperature, which in turn is partly dependent upon heat loss to the external environment.

We were interested in determining the effect of environmental temperature upon the increased activity which the rat shows during starvation. Adult male rats (350 to 400 gm) were given time to become accustomed to individual activity cages These consist of a small cage with an opening to a drum which revolves as the animal runs When a constant activity in the fed state had been achieved at any environmental temperature used, which usually took about a week, the animals were then starved, with water *ad libitum* for four days this approaches the limit of survival for starved and running rats. They were then allowed to regain their original body weight before any further studies were made In Figure 26 the average activity on the fourth day of starvation at various environmental temperatures is shown in comparison to the average spontaneous activity in the fed state. There was little change in the latter as the environment became colder When food was not available the activity increased as the environmental temperature fell. This seems to support the second hypothesis mentioned above, although there are probably other limiting factors. For instance, in view of the work of Dr Burton and others, we wonder whether shivering between 10 and 5 C becomes a more efficient way of producing body heat than straight muscular exercise

This running activity steadily increased with the duration of starvation until the fourth day at least. Curves plotted for the first, second and third days of starvation at the lower temperatures would be similar in character to the one shown here, but of lesser degree.

Sellers In Table XLIV didn t you show that animals receiving a similar diet in the cold at 2 to 5 C. died in four days if they were fasted for that period?

Stevenson Yes

Sellers Would that influence the results you obtained at the low temperature in Figure 26?

Stevenson. The imminence of exhaustion is, of course, an important

factor and you will notice that we did not run these activity studies for more than four days It should be noted that the animals used in this study were about 100 gm. heavier than those used in the acute starvation studies previously mentioned, and also they had had a week or two to adapt to the environmental temperature, whereas the acutely starved animals, not allowed to exercise, had been put in the cold on the same day that starvation was begun.

T arell Were all the observations made on the same rats?

St venson. Yes, that is, each point shown is not derived from a separate group used only at that temperature Several of the points represent the results of two or more groups at that temperature

Crismon Were none of these rats females?

Stevenson No female rats were used.

T arell What sequence was used?

Stevenson We have run into some adaptation when the temperature is steadily lowered, so in some of the studies we have adjusted the rat to the typical room temperature between exposures to the low temperatures.

Pagé Do you believe that they are running to keep warm, or is it purely an anxiety reflex?

St venson It might be said that they run as a striving towards food Another psychological hypothesis that has been put forwa d is that this represents an aimless wandering. However activity as well as food intake, may be closely related to the regulation of body temperature Dr John Brobeck and his colleagues (10) have done some work on this aspect of the problem.

S llers In my experience with that sort of experiment, I found a tremendous variation between one rat and another

Stevenson It is true. Our experience has been that in any group of twelve rats one or two w ll be unusual in that their activity is very high compared to that of the rest of the group. We have usually disca ded such individuals if their difference from the group was too great. We had one group that ran consistently more than the other ats at all temperatures studied.

Burton With egard to the activity of shivering versus extramuscular metabolic increases, or keeping warm, I should like to mention the emarkable results of Hart (11) on field mice He exercised these mice on treadmills dri en at different speeds at oom temperature, measured the blood lactic acid, and plotted this against the oxygen consumption The oxygen consumption rose to three or four times resting level As you well know after a small period below threshold, where it does not

increase with exercise, there is a rise of lactic acid So the curve is at first flat, and then goes upward.

When he puts the same mice in the cold the oxygen consumption rose to levels comparable with those obtained during exercise at room temperature. The curious thing is that in the cold he could not find any lactic acid. This may have several interpretations, but it does seem to indicate a very great difference between the mechanism of greater heat production by exercise and by shivering

Page Did he do any ketone bodies, by any chance?

Burton I think not.

Stevenson R. H. Rixon (12) has been studying some of the factors which effect movement of water across the cell membrane. Robinson (13) recently suggested that the interior of the cell was normally hyper osmotic to the extracellular fluid, and that an active outward transport of water dependent upon respiration, maintained the normal distribution of water between the cell and its environment. Robinson used rat kidney and liver slices. We have made similar studies using the rat diaphragm as a sample of muscle tissue, and have incubated it in a Krebs-Ringer phosphate medium containing 150 mg. per cent of glucose. Rixon measured the amount of water taken up by the diaphragm sample when it was incubated for 75 minutes in the Warburg appartus at various temperatures In the studies illustrated here the medium was always an isotonic (0 3 osmolar) one You will see in Figure 27 that when the diaphragm is incubated at 37 C. with an oxygen gas phase, the

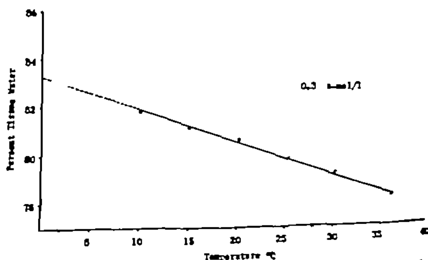


FIGURE 27 Effect of environmental temperature on water content of muscle (rat diaphragm)

tissue takes up very little water It shows a water content of about 78 per cent, which is perhaps some 1 per cent higher than when it is weighed and dried immediately after removal from the body

When it is incubated at lower temperatures, but otherwise under the same conditions, the water content steadily increases as the temperature falls, to about 83 per cent. The curve has been extrapolated to 0 C. Having made several measurements at 1 C., our impression now is that the increase is no longer linear in this region but falls off slightly We have done inulin measurements of the extracellular fluid space in these diaphragm samples, and we feel that this increase in water content is indicative of an increase in intracellular water

Crismon. I think it should be pointed out that the same thing is accompanied by a transfer of potassium from the cell interior and a penetration of sodium into the interior of the cell

Stevenson. In Figure 28 is shown the oxygen consumption of these diaphragm samples under the same conditions. The oxygen consumption decreases as temperature is reduced, and this appears to be correlated with the greater intake of water As Dr Crismon has already mentioned, there is the important point as to whether or not this movement of water is secondary to the well-known effects on ionic movement under these conditions, or whether as Robinson suggests, it is an interference with a primary metabolic transport of water

Crismon. I think it is of some interest that sodium depletion at ordinary room temperature, induced without otherwise disturbing the diet, gives rise to a disturbance of total water turnover (14)

The same phenomena, increased water intake and increased urine volume, are seen in potassium depletion when sodium intake is maintained at normal levels (15) If the hypothesis of Robinson concerning the primary transfer of water is responsible for this difference, then one has to consider it a nonspecific response to injury it must be evaluated against other hypotheses that propose failure of the sodium pump mechanism (16) and consequent upon that the retention of water

Stevenson Studies of the time relation between the water uptake and the decrease in oxygen consumption lead us to question the idea that there is an active transport of water directly dependent upon aerobic respiration.

Page What is your conclusion as to the best diet for prolonging survival?

Stevenson Our conclusion at the moment is that it does not make much difference after the first 24 or 48 hours what the previous diet has been, as long as it has been adequate. The one which gives the greatest body weight to start with would seem to be the best in view of the gen-

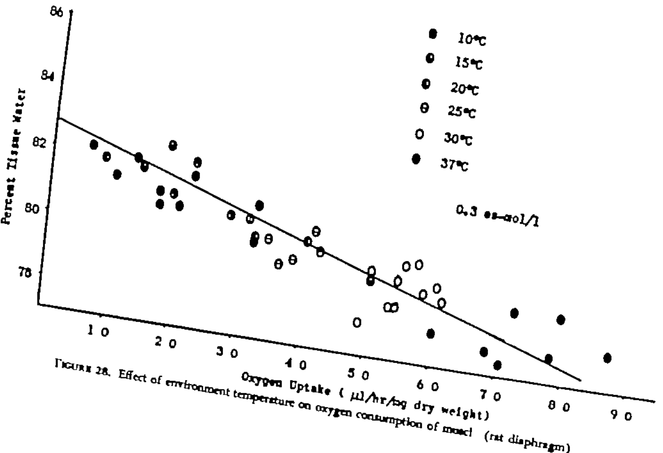


FIGURE 28. Effect of environment temperature on oxygen consumption of muscl (rat diaphragm)

cal correlation of body weight with length of survival. But as I mentioned before, although a high-fat diet sometimes seems to favor weight gain, we found that the greatest body weight loss in the first 24 hours of starvation followed a high-fat diet.

Barch Did you study the activity in relationship to starvation after the previously high-carbohydrate or high-fat diet?

Stevenson. We have not done that with a high-fat diet The starvation activity studies you saw were done with a high-carbohydrate diet. The usual or ordinary diet is a high-carbohydrate diet It takes about six months to do these studies because the animals have to be adjusted for each change of temperature.

Barton Do I understand from your results that these rats survived better when starved in the cold, if they had had a restricted diet rather than an *ad libitum* diet?

Stevenson No In those studies we were comparing survival during complete starvation with survival when some, but not enough, food was available.

Barton A little food gives no better survival rate than a lot of food? Is that correct?

Stevenson. No The increase in length of survival over that in complete starvation approaches a geometrical rather than an arithmetical relationship to the amount of food made available. Practically speaking, we may obtain more than double an increase in survival time for double the amount of food.

Crismon. Your data showed a greater contribution of body mass to survival. Have the data been corrected for the number of days involved, or is that figure you give as the total simply taken at the end of the total survival period?

Stevenson The figures I showed were the totals at the end of the total survival period. We have corrected the data, as you say for the number of days of survival It shows that the body weight loss per day is less as the amount of food a ailable becomes greater but the loss goes on longer to a final greater loss.

Crismon. Were the animals receiving some small food supplements also obtaining *potassium and sodium in their diet?*

Stevenson. They were just receiving a smaller amount of the complete diets which I described at the beginning

Crismon You have not determined how much of that over-all weight loss is water?

Stevenson No, we have not done that, as yet

Crismon Were they deprived of water or allowed water?

Stevenson They were allowed water *ad libitum* We have done another series, but only at room temperature so far in which we restricted the amount of water allowed per day (e g., 2 5 ml. per day 5 ml. per day or 10 ml. per day) and measured the duration of survival. We observed that the animals restricted their food intake voluntarily although there was always food in the cage. When we worked out the period that they survived on any one of the three isocaloric diets available *ad libitum* it was approximately the same as if their average voluntary food intake under water restriction had been given to them as a restricted diet with water *ad libitum* In other words even with food *ad libitum* these animals starved themselves to death they did not dehydrate themselves to death.

Behnke How much difference is there between a carbohydrate and a fat diet with respect to survival?

Stevenson There is quite a difference. On 5 ml of water per day which is about one-quarter of the *ad libitum* intake of these rats on a high-carbohydrate or natural diet, a rat will live indefinitely on the high-carbohydrate diet, about two or three months on the high-fat diet, and only about five weeks on the high-protein diet. So there is no doubt that a high-carbohydrate diet is the one of choice for these animals when water is short. One has to reduce the intake to 2.5 ml., about one-tenth of the spontaneous intake, to kill the rat on a high-carbohydrate diet.

Behnke I thought there was a more favorable water balance when the diet was high in fat.

Stevenson Certainly a high-fat diet should provide more metabolic water I think that diets high in fat, that is, 70 per cent of the calories from fat, embarrass the rat with ketonuria even though it is a very resistant animal to ketosis Of course, in humans, who are much more sensitive to ketosis on a high-fat diet or during starvation, there is no doubt about the value of a high-carbohydrate diet when the supply of water is restricted.

Barton It seems to me that the remarks about the rats on a restricted supply of water starving themselves to death corresponds to what Whillans and Smith (17) found in humans when they had limited water rations. One group was allowed to mix the water ration with sea water half and half and the other was not, so that one group had considerably more fluid to drink.

As I remember an interesting finding resulting from that experiment was that after the first day or so those who had the more restricted water ration just could not eat the solid rations at all, and lost a great deal of weight compared with the others. Apparently if one does not have enough water one cannot eat food.

Allen. How rigid was the water restriction for those people? Was there extreme thirst?

Barton It was fairly extreme However the ones who were allowed to mix half fresh water and half sea water did a lot better mainly because they ate better They doubled the amount of water and added some sodium chloride as well.

Coffey Was there any evidence that the rats with extremely high or low activity showed a higher mortality rate?

Stevenson No, the group was too small However it is our impression that when rats do have activity cages available, starvation is much harder on them than when they are starved without the possibility of activity

Coffey In the account of the Dachau Prison cold experiments (18) there seemed to be the suggestion that in survival, and this is of great importance to fliers forced down at sea, hyperactivity was more dangerous than if activity was reduced to a bare minimum, namely only that necessary to provide the body with food Most of the Dachau work was done in cold water tanks, as I recall.

Stevenson Our recent work has confirmed the old studies, which showed that the cardiac glycogen is in contradistinction to the other glycogens of the body it increases upon starvation, doubles, and remains high in the rat for a period up to a week, until the animal goes into extremis. This also occurs with starvation in the cold, but in our first experiment not to such a marked extent as at room temperature.

Barch That may explain the hypertrophy that is the increase in weight, because with the storage of glycogen there must be storage of water

Behnke Is the cardiac glycogen maintained at a high level in the face of strenuous activity?

Stevenson. That I do not know

Behnke In the restricted diet experiments in the cold, it would be interesting to know whether there would be any difference in survival if the same percentage of total calories required normally were fed.

Stevenson With regard to the heart, you will remember that Keys and his group (19) challenged what they considered to be the textbook statement that the heart is particularly protected in prolonged chronic starvation, and that its weight is maintained when all the rest of the body is going downhill.

Barton Is he not familiar with the work in the laboratory of the Institut für Arbeitsphysiologie?* I was there in 1945 and they showed

*Müller, E. A., Kaiser Wilhelm Institut fur Arbeitsphysiologie, Dortmund Personal communication.

me the evidence, i.e., x ray shadow pictures of all the workers hearts, and experiments in the laboratory There were about 120 subjects at the time. I saw them, and most of them were down to almost half their previous weight. They lived in a rural mountain area, where food was very difficult to obtain Their resting heart rates were down to between 35 and 40 but the hearts had not decreased in size to an extent comparable to the decrease in body weight. Their explanation was that there was less circulation required now they had lost so much weight, but the heart was relatively as large as before, so it did not have to beat so often.

Stevenson How was the heart weight determined?

Behnke It is not difficult to judge from the shadows. What about the visceral weights in individuals who have been deprived of food or who have been starved? What was the experience of the Institut für Arbeitsphysiologie? Was the heart weight maintained, say in comparison with the fall in liver weight?

Burton From my knowledge of the data they had, it would certainly suggest that the heart size was maintained in relation to the loss of body weight.

Ferrer Were these subjects anemic at this phase of starvation?

Burton. I do not know

Ferrer If they were markedly anemic, there would be a change in plasma volume and the whole relationship would be altered considerably

Burton I do not believe they had data on anemia. The subjects were not very healthy

Burch One has to be careful about judging cardiac hypertrophy from a shadow on an x ray film. It can be misleading because of dilatation.

Crismon Were the pictures made in a recumbent position, or upright?

Burton I am afraid I do not remember

Crismon. It makes a tremendous difference, especially in starvation.

Behnke Considerable data are available on people dying of malnutrition. Does this group have any information with reference to organ weights and body size?

Stevenson. The evidence from Keys (19) is that the heart deteriorates with the rest of the body certainly in animals, and he seemed to find no contradiction to that in his Minnesota experiment, or in the clinical literature which he accepted The difficulty with so much starvation literature is that we have to wait until the person is dead before we can weigh the heart, and there are so many things that occur in extremis that it is difficult to say what part is due to starvation, and what part to

other causes. His impression, as it is given in his book is that the heart does not fare any worse than the body as a whole, but it is not really protected either

Horvath It is very difficult to induce atrophy of the heart under any or all circumstances I think hypertrophy is certainly secondary to other pathological events. It is very hard to prove there is any atrophy on the other hand.

Birch Except in malignant processes

Horvath Those are very specific Outside of that it is very difficult

Ferrer Dr Stevenson, were those hearts you mentioned actually examined microscopically for size? Do we know if this is hypertrophy of individual muscle bundles?

Stevenson. No. All we know is that the heart cut off in a certain standard way at the ventricles weighed more.

Ferrer You were measuring ventricular mass, not atrial muscle mass

Stevenson Just the ventricles

Dugal How did you weigh them were they dried beforehand?

Stevenson. They were cut open washed and weighed immediately It was the straight wet weight that was given.

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THE ROLES OF ASCORBIC ACID AND SUBCUTANEOUS FAT IN THE PREVENTION OF COLD INJURY IN MAN

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AT THE DEFENCE RESEARCH Medical Laboratories in Toronto, with which I have been associated until recently we were interested in the effect of ascorbic acid on man exposed to cold, and also in the meaning of subcutaneous fat in man exposed to cold To study the problem of vitamin C we conducted two experiments one with the use of survival rations, and the other with normal rations.

In the experiment with survival rations, we had two groups of subjects, one receiving 525 mg of vitamin C per day and the other receiving 25 mg After two days at room temperature of 82 F when the subjects were fed a normal ration, the temperature of the room was lowered to 60 F The subjects were starved completely on the first day and received rations equivalent to 550 calories per day for the last nine days of the exposure period The clothing consisted of shorts, low shoes, and woolen socks There was no restriction on drinking water

Figure 29 shows one of the beneficial effects of the administration of vitamin C There was a significant difference in the skin temperature of the high- and low vitamin-C groups it was higher in the high-vitamin-C group especially towards the end of the experiment

Shumacker Where was the skin temperature measured?

LeBlan It was the average skin temperature over the body and was taken in fifteen different places

As you will observe in both groups the skin temperature increased in the morning noon, and afternoon, in some cases by as much as three degrees. In the high-vitamin-C group especially in the morning and afternoon there was some sort of cycling which resembled, to some extent, the hunting reaction One result that confirmed this difference in the skin temperature between the two groups was the subjective evidence we obtained from the subjects None of them knew to which group they belonged, since they were all getting four pills a day We asked them two days before they came out of the cold room in which group

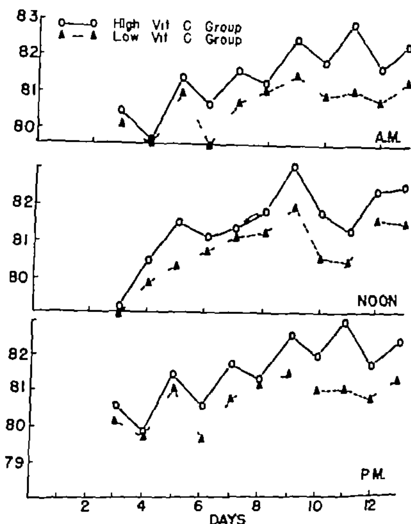


FIGURE 29 Variations in the average skin temperatures of Group I receiving 525 mg. of vitamin C per day and Group II receiving 25 mg. per day during ten day exposure at room temperature of 60 F and while fed survival rations of 550 calories per day Reprinted, by permission, from LeBlanc, J Mattet G Stewart, M and Whillans, M. G Studies on acclimatization and on the effect of ascorbic acid in men exposed to cold. *Canad J Biochem & Physiol.* 32, 407 (1954)

they thought they belonged, on the basis of comfort in the cold. In the high-vitamin-C group we had six subjects Five said they were in the high-vitamin-C group One said he was in the low vitamin-C group. Of the six in the low vitamin-C group, four said they were on low vitamin-

C intake, one was undecided, and one thought he was on the high-vitamin-C intake. The eosinophils were higher in the morning and afternoon in the high-vitamin-C group

We noticed, when the subjects came out of the cold room, that they all had some foot trouble I shall describe briefly what happened in both groups. In the low vitamin-C group the first subject had pain in walking which also kept him awake at night and this lasted for about 15 days. The next subject had swelling of the feet, with difficulty in walking for about ten days The same thing happened in the third subject and lasted for about ten days. In the fourth subject, frequent pains with soreness for about ten days were reported The fifth subject had muscular weakness with occasional pain, for eight days The last subject had sensations of pins and needles for about three days The average duration of the foot trouble was about nine days in this group

In the high-vitamin-C group the first subject had a sensation of pins and needles for about two days The same thing was observed in the second and third subjects, and it lasted two and one day respectively The fourth subject had a slight burning sensation for about three days the fifth subject soreness of the soles of the feet with some trouble in walking for about seven days The last subject experienced some muscular weakness for two days. The average duration of the foot trouble was about three days in this group compared with nine days in the low vitamin-C group

There was no swelling and no real trouble in walking in the high-vitamin-C group So from these results, that is the higher skin temperature, the subjective sensation of being warmer the higher eosinophils, and the prevention, to a large extent, of foot trouble, we may conclude that the effects of large doses of vitamin C are beneficial to humans exposed to cold.

With normal rations we did not observe any beneficial effect of vitamin C. However we had trouble in maintaining the room at 60 F halfway through the experimental period. It may be although it would have to be tested, that at colder temperatures vitamin C would increase the resistance.

In the experiment where survival rations were used, we observed some signs of acclimatization as shown in Figure 30 The urine output decreased in the cold and after four or fi e days it reached a plateau Actually these subjects were on negative water balance at first and at the end of the cold exposure period their water balance became positive In the morning, in both the high- and low vitamin-C groups, the red blood cells and the white blood cells increased at first in the cold, and then came back towards normal levels In the afternoon, the leukocytes

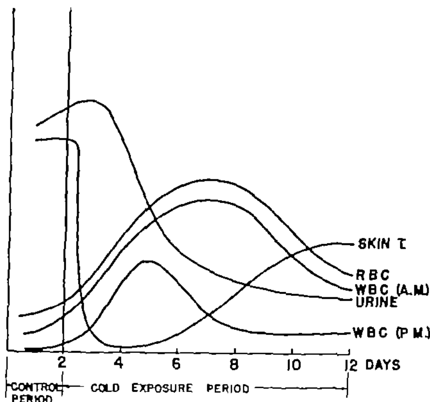


FIGURE 30 Signs of acclimatization observed in men exposed for ten days at room temperature of 60° F while fed a survival ration of 550 calories per day

repeated the pattern of the morning, but they came back to normal levels faster in the morning

The skin temperature changes may be explained, to a certain extent, by the fact that the subjects lost weight in the cold, and consequently lost some subcutaneous fat. As we have shown in another experiment, a few millimeters of subcutaneous fat may mean the difference of a few degrees in the skin temperature that is, less fat would mean a higher skin temperature

Burton What was the normal control urine output in the warm, before the experiment?

LeBlanc The normal output would be about 2,000 milliliters

Burch What was the lowest urine volume during the cold exposure period?

LeBlanc This would be 400 to 500 ml., and the water intake would be between 600 and 700 milliliters The water intake is lower at first,

ben the volume is about 400 ml., and goes up gradual t about 700 ml.

Birch Did you do any blood chemistry to le n th. l 1 nitrogen, or nonprotein nitrogen, at such a low output

LeBlanc We did some nitrogen ketone body determin t n 1 uri

Birch But not in the blood?

LeBlanc No

Stevenson. What was the intake?

LeBlanc The rations were exclusively carbohydrat

Allen What is the daily requirement of vitamin C the u

LeBlanc Twenty-five milligrams is the minimum dose n l, r instance, by the British National Research Council

Brown Were both groups allowed to drink all the water the art

LeBlanc Yes.

Brown. Why was it that the urine volumes were so high bef re they went into the cold?

LeBlanc At first they were not on survival rations the control period was with normal rations We fasted them completely on the first day in the cold, and for the remaining days they received 550 calori s

Brown I understand that, but there is no scale there, and you put the average urine volume considerably below the peak of the urine output curve during those first two days before they went in the cold

Barton I think the way the curve is drawn is misleading They did not go into the cold the second day so the curve should really be horizontal until they reach the vertical line.

LeBlanc The part of the line corresponding to the control period should be a straight line parallel to the horizontal axis.

Barton. Similarly with the red blood cells. They did not really rise until the subjects went into the cold, so the line should be horizontal for the first two days

Brown I am interested in the point about skin temperature and subcutaneous fat. Is the average skin temperature of the obese person lower than that of the thin individual?

LeBlanc We had six subjects We took the thickness of the subcutaneous fat over the trunk in 20 places, and made skin temperature measurements. We exposed the subjects for an hour at three different temperatures, i e., 70 60 and 50 F

Our first finding was that the fat thickness explained the regional differences in the skin temperature. For instance, the fact that the abdomen was colder than the chest, and the front colder than the back, especially in fat subjects, was explained by the difference in fat thickness.

Allen Did you tell the subjects that some of them were going to withstand cold better than the others?

LeBlanc We told them this experiment was to study the effect of vitamin C, and that it might have a beneficial effect. The pills used in the two groups were of different colors They may have discussed this between themselves, but they did not know which pills had the vitamin C.

Talbott Did they have any basis for comparison, such as being warmer or colder? Did you reverse the procedures of the two groups at any time?

LeBlanc No I think what they probably did was to compare their degree of warmness or coldness with the other subjects

Stevenson Were they concerned about the condition of their feet?

LeBlanc They did not have any trouble with their feet before they came out of the cold room

Allen Do you think it might have been better not to inform them that they were test subjects taking vitamin C to determine their reaction to cold? Would the data have been more accurate in that case?

Horvath. It might have influenced their reactions.

LeBlanc We wanted our subjects to have a base of comparison because they had never experienced an exposure of that nature before At any event I do not think that the suggested alternative would have modified the objective evidence favoring the use of high vitamin C doses.

Barton You mentioned the second experiment in which you gave an adequate diet rather than the survival diet. I think you said you could see no protective influence of vitamin C there. We should be interested to know whether the subjects on an adequate diet had any foot trouble

LeBlanc No foot trouble was observed in that case. I might say that with the normal ration we had a postexposure period. The subjects were kept in the same room at 82 F and they did not walk around as much.

Allen. Did the interviewers of these subjects know whether they had 525 or 25 mg of vitamin C? That would make a tremendous difference.

LeBlanc No, they did not know However it was quite obvious by looking at these people which ones belonged to the low vitamin C group For instance, one could scarcely walk, and the swelling I mentioned was quite noticeable

Brown. I understand the peripheral nerves were not examined in the feet.

LeBlanc No

Brown Could you tell us in what way there was difficulty in walking? Was it tenderness or pain in the feet or the calf of the leg discomfort on movement of the joints, or muscular weakness?

LeBlanc They were examined by their own medical officers. I reported all the observations that were given to us.

Brown They were not under your supervision, then?

LeBlanc Not at that time.

Birch Were the clinical manifestations different from scurvy? Did the people on the 25 mg dose of vitamin C have a mild amount of scurvy rather than cold injury?

LeBlanc It may be that it was a combination of two or three factors. These clinical manifestations may be identified, to a certain extent, with hunger edema, trench foot, or symptoms of scurvy

Allen If the 25 mg were adequate, they could not ha e had scurvy It is not possible, is it, to develop scurvy in ten days?

Horvath It takes six months or more

Talbott Even with the aggravation of cold I do not think it would be possible to develop scurvy in that short time with 25 mg of vitamin C being given.

Horvath One sees similar symptoms whether a subject is on a high-vitamin-C diet or not such as pain in the feet. It is partially joint pain, and there is a hyperesthesia which lasts longer with some people than with others.

Barton One sees it even if they have had an adequate diet?

Horvath Yes these people I mention were being given 3 600 calories per day and they were doing nothing except to be exposed to cold. I do not know whether it is helped or made worse by variations in the content of the diet, but at least we do see pain in feet in normal individuals when they are given what is presumably an adequate diet.

Brown Dr Horvath, what is the basis of the edema

Horvath I think it was because we kept people lying on cots The only time they got up was in order to defecate

Allen Quite the contrary to lie flat is the poorest way to develop edema of the extremities.

Horvath It may have all been due to the cold We cannot reach any conclusions because we did not see it in everyone If it had been observed in all individuals so exposed, we could give some sort of rationale for it. The amount of edema which appears on the first day of transition is quite variable. Some people may have a marked pitting edema, while in others it is barely perceptible

Brown The edema appears the first day?

Horvath It occurs after they have been returned to warm en ironment.

Brown It is not a form of cold injury?

Horvath It might be. I think it may be similar to immersion foot, except broader in extent

Travell In these subjects did the swelling occur during the exposure to cold?

LeBlanc No after the cold.

Stevenson Do chilblains appear in a warm environment?

Horvath Yes

Birch Did the patients manifest a good deal of hyperemia when they were brought into the warm environment?

Horvath They showed some but I would not say very much. I think it is variable. If we experiment with 12 subjects at a time, we see it in three or four of these people, and they vary tremendously in degree. In the one experiment in which I was a subject, I had edema which was quite marked, extending just above the ankle I would say it was a good, strong pitting edema. It disappeared after about eight hours that is, it became imperceptible, but the pain in the feet on walking, and the hyperesthesia, persisted for four or five days

Shumacker Does numbness of the feet develop when they are exposed?

Horvath I think that is a little difficult to answer At an ambient temperature of 60 F in the nude there is a certain amount of numbness to all parts, I think I am sure I was cold, but I do not believe I noticed any particular numbness

Travell Was there deep tenderness of the muscles or only cutaneous hyperesthesia? The skeletal muscles might be responsible for some of the pain We have found that muscle pain and stiffness are sometimes benefited by large doses of vitamin C, i.e., 500 to 1 000 mg per day

Horvath It was all in the foot most of it was deep in the initial stages, but it gradually became less noticeable as time went on.

Allen Did you observe changes in skin temperature of the extremities, since it seems apparent that the fluctuations over the trunk would be less marked

LeBlanc I would not like to say without referring to the original data, but I think changes in skin temperature occurred in the trunk rather than in the extremities

Editor's Note Dr LeBlanc would like to add the following comments to his remarks at the conference.

> In both groups studied, the increase in skin temperature was approximately the same for all parts of the body The difference between the high and low vitamin-C groups was especially obvious on the cheek, upper arm, thigh, and abdomen. A striking similarity between these parts mentioned is the larger amount of subcutaneous fat found there.

Horvath The weighing factor so far as the extremities are concerned, is I suspect, a small fraction. The weighing fraction for determining the mean skin temperature makes the extremities very small. I presume you would use about 0.06 of the total 100 per cent for the extremities, would you not?

LeBlanc Yes.

Allen. What I meant was, in the calculations would marked changes in temperature of the extremities be diluted in the total?

Horvath Yes.

Barton Will you be able to retrieve that from the data?

LeBlanc Yes, I think so

Barton It seems to me, from the experience of other people that changes in skin temperature might be more marked in the extremities. It would be well worth looking for that in the data.

Bebnke Dr Horvath, what is the basis for the injury that occurs at 60 F? Is it the result of excessive vasoconstriction?

Horvath We have seen so few subjects that I cannot answer your question directly The temperatures of the feet and of the hands are very close to environment as you would anticipate at 60 F I know there is considerable vasoconstriction maintained for 24 hours every day during those five days. Beyond that I have no real basis for judging

Allen From what you have said, it is quite apparent that changes in the extremities were quite marked If they approach ambient temperature, and the average skin temperature was retained at 22 C. there must have been marked changes in the skin temperature of the extremities.

Horvath. Yes, in terms of Fahrenheit, it was roughly around 62 during the exposure, and probably in the high 80 s and 90 s part of the time, depending upon the environment There was a marked vasoconstriction. But as I say it does not occur in all individuals

Bebnke In the same type of experiment, Newburgh (1) exposed nude individuals in an environment in which the ambient temperature was 60 F These individuals were up and about Several of them developed foot injury The same type of injury may be produced by immersion in cold water at 6 C. for a period of 30 minutes, but in one individual it did not occur at 10 C. after several exposures of about one hour each. Perhaps the basis of the injury is the deprivation of the blood supply rather than the cold *per s*

Shumacker It sounds very similar to the mild cold injuries that we observe sporadically You did not have vesicles in these, however Did the subjects who complained of pain or swelling develop vesiculation of the skin?

LeBlanc Not that I know

Horvath The degree of injury seems mild, but it looks somewhat like the type one sees in the immersion syndrome.

Burch Will you tell us how you measured tissue thickness?

LeBlanc By taking a fold of skin and using calipers We made sure the two layers of fat were close together and applied a slight positive pressure.

The three curves shown in Figure 31 represent the insulation, in Clo, after one-hour exposures at 70° 60 and 50 F At 70 F as you

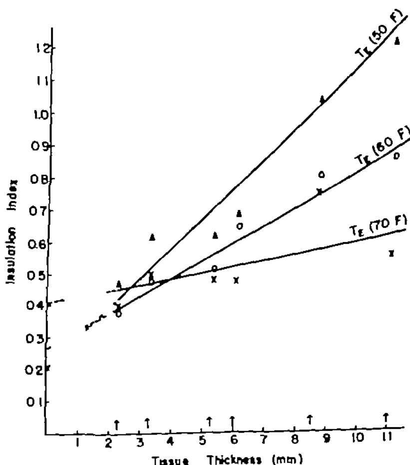


FIGURE 31 Insulating value in c/ of subcutaneous fat after exposure of one hour at 70 60 and 50 F Reprinted, by permission, from LeBlanc, J Effect of subcutaneous fat on skin temperature. *Canad J Biochem & Physiol* 32, 354 (1954)

observe, the insulation provided by the fat was not very high, but when the temperature was lower the body seemed to utilize the fat layer more efficiently This is obvious at 60 and more so at 50 F The individual with 2.2 mm. of epimuscular tissue probably has not much subcutaneous fat. In this subject the insulation was not changed as the room temperature was lowered from 70 to 50 F In contrast to other subjects who have subcutaneous fat it may be said that the insulation of the skin was maximum at 70 F

This corresponds to the findings in Dr Burton s experiments in which a minimum blood flow at 70 F was demonstrated. We have calculated what would be the insulation of one inch of fat at these three different temperatures. At 70 F one inch of fat would provide an insulation of about 0 4 Clo at 60 F 1.2 and at 50 F about 2 Clo

Burton Would you agree that your draftsman has made a mistake in drawing the dotted lines going to the origin? This index measures the total insulation from the core of the body to the surface, and only part of that is subcutaneous fat So those lines for zero fat thickness should not reach the origin, but be at some residual value that is the insulation of the rest of the tissue, which is not subcutaneous fat. I think they are rather misleading they should be straight lines meeting with an intercept, which is insulation of the remainder of the tissues between the core and the surface. They do represent the contribution of increasing amounts of subcutaneous fat, but they should not go down to the origin should they?

LeBlanc I agree. But I think the broken line shown on the figure corresponds to the insulation of the skin.

Burton: The index measures the total insulation of the tissues from the core of the body where the temperature is presumably uniform, to the surface. I think 0 3 of a Clo of that is before one gets up to the skin, and after that the rest of the insulation depends upon the subcutaneous fat.

LeBlanc It intersects somewhere between 2 and 3 Clo

Burch. Are the insulation effects of fat due primarily to the tissue itself or because it is avascular?

LeBlanc I do not think this change could be attributed to the fact that there was a decreased blood flow or asoconstriction, because the fat tissue is very poorly vascularized. It is probably a gradient that sets in at 60 and 50° F but which is not observed at 70 F

Behnke I have some data on that point from calculations of Gersh and Still (2) which indicate that the capillary surfa e in what may be termed lean fat tissue is four times greater than it is in fat-rich fat tissue That is to say the fat insulates the blood vessels, so I think the effect may

well be a vascular one. In other words if the fat is removed one then exposes a greater peripheral vascular area to cold One should think of the insulation not in terms of a piece of clothing, but rather as the protection of the blood transported via blood vessels.

LeBlanc Do you think that would explain the large increase in insulation that I observed when the room temperature was dropped from 70 to 50 F? It was a fivefold increase.

Behnke No I merely offer it for consideration. The specific arrangement that affords insulation may consist in large part in the insulation of peripheral blood vessels

Burton The fact that fat is less vascular than other tissue would mean its insulation would probably depend more upon vasoconstriction and vasodilatation than other tissue. In other tissues where there is considerable water and no fat one has the variable factor the transport of heat by the blood stream, so to speak, in parallel with actual conduction through the tissue Therefore, an increase of blood supply just adds on some more transport of heat to this physical transport through the tissue. But in fat tissue I think the change in insulation is more likely to be because the fat itself is a very poor conductor until it has some blood supply which lowers the total insulation

Because it is relatively avascular I would have thought that a change from vasoconstriction to vasodilatation would be likely to produce a greater change in the insulating power of fat than even in other tissue. I would be inclined to think this change in the insulating power of fat between 50 and 70 was actually a vascular change.

Pagé In the sense of vasoconstriction at 50?

Burton. Yes but this is a matter of interpretation. I think these curves are really quite remarkable because from their slope, for the first time in an *in vivo* experiment, we can deduce the insulating power of human subcutaneous fat

Behnke These are calculations, are they not, rather than experimental data?

LeBlanc They are calculations from the results we obtained with skin temperature measurements

Burton. Hatfield and Pugh (3) working with Dr O G Edholm, of the University of Western Ontario, made a good many measurements on fat of animals, human fat, and other tissues of humans *in vitro*? But I think this is the first time the experiment has been done *in vivo*

Coffey Dr LeBlanc, in Figure 30 we saw an increase in skin temperature as the subject spent more time in the cold room Was there any suggestion on the part of the subjects that they were becoming better adjusted to the situation they were living in?

LeBlanc. Yes. On the second day of cold exposure we asked them to estimate the degree of discomfort caused by cold, hunger and confinement. They all rated cold as being worst, hunger second, and confinement third. But at the end they thought hunger was worst, cold second and confinement third. It may be, however that they were hungrier toward the end of the experiment.

Brown. There is an interesting point there. The diminution of the discomfort in some experiments has not paralleled the skin temperature. With continuing low skin temperature, discomfort is greatly alleviated and disappears.

Coffey. I have observed between 25,000 and 30,000 man-days in the cold at temperatures from –20 to –60° F. In examining the cold injury which did occur which was a very small percentage, it was always apparent that the injury could probably have been prevented had the proper precaution been taken. One would assess this as negligence at the first glance. But after looking further into the injuries a pattern seemed to emerge which could be associated with the fatigue of the individual. When he becomes fatigued he may lose the ability to take proper precautions for protection against cold injury. So it is essential that we develop methods of training and types of equipment that reduce, as far as possible, the fatigue which is experienced under Arctic cold conditions. If some method of measurement could be devised which would give an evaluation of the level of fatigue that an individual was experiencing, it would be of great value. I wonder if there is any physiological measure which could be used for this purpose.

Dugal. Did you notice any change in shivering, for instance, from the beginning of exposure to the end?

LeBlanc. They shivered more at first than towards the end of the exposure. That was made evident by their subjective sensations.

Stevenson. When men are in the cold for days, as during your experiment, is there, apart from the shivering, any change in their activity if they are not under instructions in this regard? Do they move about more at the beginning or at the end of the period?

LeBlanc. They move less when comparing the control days with the cold days. When the cold period started they became quite inactive especially with the survival ration.

Barton. Did you find a progressive rise of skin temperature in the cold with adequate rations?

LeBlanc. As I mentioned, we had trouble maintaining the room temperature. We had to take the subjects to a colder room and allow them more clothing. Up to the middle of the cold exposure period, there was no indication that the skin temperature would increase.

Pagé What were the actual differences in temperature between the experiments with the survival ration and the normal ration? Was it cold during the later experiment, or was the temperature rather high?

LeBlanc We started at 60 F with a normal ration as well as with a survival ration, but we could not maintain that temperature in the room.

Pagé How high did the temperature go?

LeBlanc To 70 F We decided then to expose the subjects for three hours in the morning and three hours in the afternoon at 5 F They had some clothing on. Between these exposures they stayed in the room at 70 F

Sellers I agree that measuring the insulating capacity of the skin and subcutaneous tissue is probably of considerable practical importance Therefore, I should like to know just how you measured the tissue thickness at the different temperatures, and whether those points were from the same individuals or from different groups.

LeBlanc The same individuals were used for the three different exposures. The three points corresponding to a fat thickness of 11 mm. for instance, were from the same subjects.

Sellers What part of the body was used?

LeBlanc The trunk. *We made measurements at 20 different places* on the trunk.

Burch How did you draw the lines between the points?

LeBlanc *It was regression.*

Burch Was this calculated?

LeBlanc Yes

Brown *How was the insulation index calculated?*

Burton The derivation of the insulation index Dr LeBlanc used should be explained Heat, of amount *H*, is *flowing out from the core of the body to the skin, and the same heat, supplemented by evaporative* heat, and totaling H′ is going from the skin to the environment. If the environment temperature is T_a, the skin temperature T_s, and the core temperature T we can write two equations. *One is for the transfer of* heat from core to skin, and the other from skin to environment. First of all, the difference of temperature that is driving the heat flow H is (T − T) Divide this by the *insulation of the tissues*—the insulation *all the way from the core to the surface*—and the result must be the heat flow H

From there on it is not quite the *same heat flow* because there is a bit added to it, namely the evaporative heat The total, H′ must equal (T − T) over the insulation of the air from the skin to environment. Perhaps I should say plus the *insulation of the clothing*, but it does not apply in this experiment. Were the subjects lightly clad?

LeBlanc They were nude.

Barton Let s say that I is the total insulation from the skin on. If we divide one of the equations by the other we obtain the ratio I_t to I_s of the ratio of the insulation from core to skin which is the physiological variable, to the insulation from the skin on which is a physical variable, depending on the clothing and wind velocity

The equation for heat flow from core to skin is

$$I = \frac{T - T}{H}$$

And for the heat flow from skin to environment

$$I_s = \frac{T - T}{H'}$$

So the ratio $\frac{I}{I_s}$ will be $T - T_s$, which is the internal drop of temperature, over $(T - T)$ the external drop of temperature, multiplied by the ratio of H to H, as below

$$\frac{I_t}{I_s} = \frac{T - T}{T - T} \times \frac{(H)}{(H)}$$

In 1934 this appeared in the *Journal of Nutrition* (4) although there we were not using insulation, but the reciprocal the conductivity

The ratio, $\frac{H'}{H}$ if sweating is not taking place, is rather constant because as you know the proportion of evaporative loss from the skin is a fairly fixed proportion of the total heat loss from the skin. This ratio is normally 1.21 Making the assumption that in these experiments this ratio did not change, we obtain an index of the changes of insulation of the tissues by taking just the ratio or the internal drop of temperature to the external drop That, I think, is all Dr LeBlanc has used, and he has turned the equation into this ratio, which could be called the insulation index. He multiplied by I_s and assumed that the constant was 1 21 Then because he knew the value of I_s from the air movement in the chamber in Clo units, he was able to calculate I_t

$$I_t = \frac{T - T}{T - T} \times (I_s) \times 1\ 21$$

All we have to know is the rectal skin, and air temperatures, and multiply by I_s.

LeBlanc We used 0 8

Barton We assume this to be 0 8 Clo units, which is perhaps high,

but correct for fairly still air This value I is what he has plotted. It seems to me it is the ideal way to distinguish the *physics from the physiology* and to interpret skin temperature, because this index automatically separates the two and gives us the changes *in the physiology Normally* it depends on the circulation. In this case it depends more on the subcutaneous fat. Just *by taking the ratio which I called the thermal circulation index,* we could separate the physics from physiology

Burch Would you encounter difficulties with these calculations if blood were circulated to the subcapillary vessels of the skin in such a manner as to shunt straight through the insulating pad?

Burton. This over all figure for the insulation of the tissues is the end result of straight physical conduction.

Burch In the measurements we have been doing the skin blood vessels, when dilated, would approach the liver temperature or rectal temperature, and we might have the impression that perhaps there was not very much insulation by the subcutaneous tissues, when actually it would still be there but not functioning as well as had been calculated.

Burton Any acute changes that a given individual may show have to *be interpreted as changes in the peripheral circulation. I did measure the* effect of thermal conductivity of the skin with different degrees of circulation *This can be done in the finger where the total circulation can be* measured, which is the skin circulation. It gives a nice correlation. One *obtains a straight line with moderate scatter Between vasoconstriction* and full vasodilatation there is approximately a doubling of effective *conductivity to the outside of the skin.*

Burch Have you conducted an experiment with a full thickness of skin, *including the subcutaneous fat, wrapped around a source of heat* in order to study the insulating effects?

Burton No I have not. In your hospital you would probably have subjects where you could do that, but in my laboratory there would not be subjects available *with sufficient* fat.

Burch I meant *in vitro* studies, using skins obtained on the autopsy table.

Burton Hatfield (3) has done a lot of this sort of thing, has he not?

Burch Such skin *may be readily obtained.*

Burton. In *in vitro* experiments there is no circulation. That is why I think *Dr LeBlanc s experiment is* so valuable it is, I think, the first *in vivo* measurement of the insulating power of fat.

Carlson Didn t *you previously* call this circulation index ? What is there in this experiment that makes the *insulation all fat?*

Burton That *was my point* with Dr LeBlanc s Figure 31 I think the dotted lines should be eliminated because the straight lines all have an

intercept which is the insulation of the rest of the tissue from the core to the surface. It is only the end part that depends on the subcutaneous fat, and it is just that section which increases in the fatter subjects

Carlson Suppose you were able to vasodilate that area, what would happen?

Burton The total insulation of the tissues would go up about five or six times between construction and dilatation

Burch That is the recorded insulation, but the actual insulation should not change

Burton I am using insulation as a measure of the difficulty of heat transport.

Burch It is comparable to insulating a man by placing hot oils around him. He would lose very little body heat under such circumstances because he would be protected by that source of heat placed outside

Behnke Why not use the numerator the difference between the deep temperature and the skin temperature as the measure? What does the denominator add?

Burton The ratio has to be used, if there is any question that the actual flow of heat has changed For instance, during exercise or in the cold, there may be three times as much flow of heat H may be three times as great.

Behnke Under these conditions, is there any reason to believe that the denominator changes except as the common term changes

Burton I think it does change in experiments at different temperatures. The *reason for using the ratio is to eliminate the H, which is* unknown, unless one does direct calorimetry as Prof Henry Bazett and I did in bathtubs. We made a calculation of the same kind If the H changes two or three times one does not get an idea of the insulating power one must take a ratio. Also between constriction and vasodilatation, if we take different areas of the body say the trunk and extremities, the trunk will be at 35 even if the subject is constricted when he is fully dilated it will not go much higher than 36 5 C., whereas the same degree of dilatation will change the temperature of the toes from 23 up to 33 That does not mean there has been a greater change in circulation in the extremities than in the trunk If we take the insulation index, we find the ratio has changed by about the same amount in the two cases, which separates the physics from the physiology very neatly I think

Talbott To go back to the vitamin C experiment again, the subjects, before the experiment, were on house diets or regular rations. They presumably all started off at the same level of vitamin C?

LeBlanc They were on a mixed diet before the experiment.

Stevenson Regular army rations?

Talbott They are usually fairly high in vitamin C.

Stevenson Individual food preferences might produce deficiencies even on a generally adequate diet. These soldiers probably had the same opportunity for proper nutrition that a civilian living on a good civilian diet has

Allen What is the vitamin C content of let's say the average diet, or the camp diet?

Stevenson I should guess from 75 to 100 mg at least.

Sellers When dietary surveys are carried out at installations like this, it always surprises me how many differences there are between various sections of the country apparently depending on local administration, food supplies, or perhaps even differences in the vitamin content of the food. I imagine everyone here is familiar with that sort of data. At one place the daily intake will be 50 and another place it will be 120, a large difference.

Horvath This ration would provide a fixed amount of vitamin C, would it not?

Stevenson. The ration scale for a static installation provides such a wide choice of foods for the dietitian making up the menu that all we can say is, that each ration, if used in chance fashion, over a period of a month or two will provide an average amount per day of the necessary food elements.

Horvath In other words, the chances of a C deficiency appearing would be very small.

Sellers Extremely so

Stevenson One would have to have the worst cook and the queerest food habits for this to happen.

Allen. It is possible, though.

Stevenson Those things have occurred together

Allen We have seen three cases of scurvy well documented in the Middle West, one within 20 miles of Rochester Minnesota. They were people with peculiar dietary habits

Sellers Many years ago I saw a case in a market-gardener you would think that would be the wrong business in which to develop it.

Burch We frequently encounter malnutrition in old people who have peculiar eating habits

Stevenson Dr LeBlanc, the vitamin C subjects were soldiers living in Toronto, were they not?

LeBlanc In the experiment with survival ration, they were Canadian Air Force personnel living in Toronto

Stevenson Anyway they were at Toronto, and not at Fort Churchill

Talbott Then there is an even higher probability of obtaining adequate vitamin C.

Stevenson In what part of the year was the study done?

LeBlanc The survival ration study was done in October and the normal ration study in May

Stevenson Just after a good fruit season.

Coffey Dr LeBlanc, regarding the skin-temperature measurements in Figure 29 on the eighth day I noticed in the two groups that the temperature seemed to converge and there was no significant difference between them. Was there anything unique about this eighth day? Was there a break, for example, in the exposure?

LeBlanc Do you mean why was there no difference between the low and high-vitamin-C groups?

Coffey Yes the morning and evening reports, I think, were identical and the noon record showed only a small difference

LeBlanc There was always a difference between both groups morning, noon and afternoon

Coffey At least during the convergence, the two points were very close in Figure 29 There was no break?

LeBlanc No, there was continuous exposure

Crismon Do you interpret the increased skin temperature in the high-vitamin-C group as representing some direct effect of vitamin C on the ability of vessels to dilate under the stimulus?

LeBlanc It is probably that. I cannot find any other reason because they all lose weight at the same rate, and fat thickness probably could not explain the difference between both groups

Allen Are there any data on the effect of blood flow under basal conditions of let us say the intravenous injection of vitamin C?

Crismon Yes, there are animal-experiment data on scorbutic guinea pigs. The phase preceding capillary hemorrhage, or at least, hemorrhage in the pre venular circulation, is characterized by relatively sluggish activity of the vessels, and failure to respond to either intravenous doses of epinephrine, or topically applied epinephrine (5)

Horvath There was a method of increasing blood flow in patients with peripheral blood vessels by giving injections of ascorbic acid intravenously

Allen That was merely supposed

Horvath Yes I do not think it was finally determined but at least there is a report on it in the literature (6)

Allen. Dr Crismon, are there any studies on controlled blood flow?

Crismon No

Allen On skin temperature?

Crismon. There were some incidental observations of perfusion rate in isolated legs taken from guinea pigs that had scurvy and from those that were normal, in which flow rates were higher in the scorbutic animals: they did not reveal the rhythmicity of flow or cycling that was observed in the legs from normal animals. It was not repaired by the simple addition of ascorbic acid, but by using crude sources of vitamin C. It is related, I think, to the studies Szent-Györgyi (7) reported, in which some of the flavonoids were thought to represent vitamins. The work I refer to was done by a Russian investigator Selezeneva (8) in 1941.

Coffey. Have you any data on heart rate or pulse rate over this period?

LeBlanc. The pulse rates go down in both groups in the cold.

Coffey. Over the twelve-day continuum, was there any change in the rate? Was there a trend up or down?

LeBlanc. There was no significant change.

Dugal. Does the pulse rate go down when normal rations are given?

LeBlanc. Yes.

Coffey. The differences between the two groups, though, were not significant.

LeBlanc. That is right.

Brown. Does the skin temperature go down as much with the normal ration?

LeBlanc. I think it is comparable at first.

Sellers. The experimental procedure is really not comparable, is it?

LeBlanc. That is right.

Crismon. A question was raised in one of the previous meetings concerning the work on isolated tissues, as to whether or not *in vitro* studies could show evidence of survival of tissues frozen for varying periods of time. Comparisons were needed between tissues frozen after detachment from the body and those that had been frozen while still attached to the animal.

One of my associates, Dr. Frederick A. Fuhrman,* has carried out such experiments on rats, in which skin from the dorsum of the foot was removed and subjected to cold for varying periods of time. Its oxygen consumption was then measured in the Warburg respirometer. He studied varying levels of temperature.

Burch. What was the thickness of the skin of the foot?

Crismon. The skin of the dorsum of the hindfoot is sufficiently thin that its oxygen consumption in relation to thickness satisfies the so-called "Warburg limit" of oxygen penetration per unit rate of metabolism, and it is not necessary to do any further slicing or damage.

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*Fuhrman, F. Personal communication.

Burch There was not any subcutaneous fat or connective tissue? Were these tissues removed by dissection?

Crismon I did not see them prepared, but it is my impression that there was very little material there that could be removed without a good deal of trauma. That additional trauma was avoided.

Table XLVI refers to skin taken from the feet of rats after immersion in a −25 C. freezing solution

TABLE XLVI

The Q_{O_2} of Skin from Rat Feet Frostbitten at −25 C.

FB*	Days After FB	Q_{O_2} Dry Weight	
		Normal	FB
15 seconds	3	2 00	2 53
60 "	1	2 5	1 72
60 "	2	2 07	2 36
60 "	3	2 10	3 40

* Duration of the frozen state

The time of freezing was measured in seconds from the instant that whitening of the foot was noted. The rats were lightly anesthetized with pentobarbital. Dr Fuhrman informed me that his past experience indicated that the rats signal when freezing occurs by a loud squeak. I think this probably corresponds to Siple's ping in the cheek (9)

At any rate, the times expressed in the first column of Table XLVI are from the time of freezing until the foot was removed from the freezing solution. The animals were returned to their cages for a varying number of hours. Then skin from the normal foot was compared with skin from the frostbitten foot of the same animal. The Q_O's are expressed in terms of milliliters of oxygen per gm of dry weight per hour

The normal values of Q_{O_2} range from 2 0 to 2 57. One day after frostbite involving 60 seconds immersion in the freezing bath after the freezing occurred, the Q_{O_2}'s were 2.57 for normal skin and 1 72 for frostbitten skin. The frostbitten tissues had a Q_{O_2} of 2 53 three days after 15 seconds of freezing, and 3 40 three days after 60 seconds of freezing

The thing that interests me in this work is that the Q_{O_2} values in-

creased over a period of three days In animals injured for the same length of time there is a progressive rise of Q_{O_2} in the skin samples. This value represents a mean from six samples of skin for each temperature and time Something apparently has appeared in the skin sample taken that is responsible for oxygen uptake at a higher rate than is characteristic of normal skin.

This cannot be due to the presence of bacteria if it were, the graphs for oxygen consumption rate over the three-hour period of a single run would show an upward drift owing to the growth of bacteria. That is not the case they remain quite level, but they are consistently higher

EDITOR'S NOTE Dr Crismon would like to add the following comments to his remarks at the conference.

> The upward drift of Q_{O_2} might not serve to indicate the presence of bacteria if they were not undergoing rapid growth Subsequent work in Dr Fuhrman's laboratory has indicated the presence of yeast like organisms in scrapings from frostbitten skin of rats three days after frostbite. The quantitative contribution of these organisms metabolism to the over-all oxygen consumption of frostbitten skin has not been determined.

Crismon Table XLVII shows what happens to skin if it is taken from a normal rat, frozen after it is detached and then the oxygen consumption measured Here the temperatures used were +1 —4 and on down to —25 C. The hours here represent the duration of exposure.

TABLE XLVII

The Q_O of Rat Foot Skin After Cooling *in vitro*

Temp. (C)	Time (hrs)	Frozen	Q_{O_2} as Per Cent of Control
+ 1	3	—	108
— 4	22	—	106
—10	1	+	83
—10	3	+	58
—10	5	+	42
—25	1	+	23
—25	3	+	9

There are minus and plus signs to indicate whether or not freezing occurred in the skin.

At these temperatures +1 and −4 C., no freezing occurred These data are expressed in per cent of control alue The QO_2 of normal skin would be approximately 2 00 equal to 100 per cent at lower tempera ture, and for longer periods of time there is a progressive fall of oxygen consumption.

The increase of QO_2 that was seen when the skin was attached to the animal during and after freezing, does not occur in skin frozen after it is removed. There is nothing in the skin prior to freezing that responds to cold by an increased rate of oxygen consumption. This is obviously the declining oxygen consumption represented by progressive destruction of metabolic units.

Later on we hope to have some data from Dr Fuhrman which will permit us to identify histological changes in the skin that may help to account for the increased oxygen consumption during the recovery period.

In the animals that were frostbitten while the skin was attached, the frostbite was not severe enough to produce gangrene in the dorsum of the foot the toes of the foot from which the samples were taken devel oped gangrene and had to be removed

Dr. Fuhrman is running a second series now with longer freezing time to see whether he can find an injury level that will produce gangrene of the dorsal foot skin in untreated rats and survival of such skin when the immediate rapid warming treatment is used.

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APPENDIX AUTOBIOGRAPHICAL SKETCHES OF PARTICIPANTS

JANET TRAVELL: I have been particularly interested in cardiac pain, and the interrelations of somatic trigger mechanisms and referred visceral pain. In the Department of Pharmacology Cornell University Medical College, we have studied the effects of cold in the form of ethyl chloride spray and other rapidly cooling agents, on pain and trigger areas that develop secondary to trauma or visceral disease This was not so much in connection with the local anesthetic action of these agents, as with the counterirritant or reflex effects of intermittent cooling on thermal burns, so we ha e an interest in cold and tissue injury which we are pursuing at the present time

JEFFERSON M. CRISMON: In the Department of Physiology Stanford University we engaged in work on gangrene resulting from cold injury during World Wa II Since that time my interest in cold injury has persisted, although actual research in that immediate area has been confined to ancillary topics related mainly to control of small blood vessels I participated as a consultant in the organization of the military research group that was sent to Korea, where an attempt was made to work out some problems in the field My associate at Stanford Dr Frederick A. Fuhrman, is still continuing with work on cold injury my own work is in connection with capillary blood flow

EDOUARD PAGE: My interest in cold goes back to the war years, when I had the privilege of joining Prof Henry C Bazett s team in Toronto. I worked mostly on protective clothing for the Canadian Air Force with Dr Burton of this Conference and Dr J A. Kitching, now at the University of Bristol, England From there I moved to Quebec and could not resist Dr Dugal s fine animal cold rooms I have been working on metabolism in rats in connection with adaptation to cold for the last five years

STEVEN M. HORVATH Dr Talbott is partially responsible for my interest in cold. The army has continued it, nd we are still working on the problem, except on a sl ghtly different level than we did many years ago This meeting has particular significance for me because I was here at Fort Churchill about eight or nine

years ago One observes the tremendous improvement that has taken place in both the facilities available for research, and in the protective articles that are now available. I think in the past too many people studied cold exposure by staying in the warm.

HARRIS B. SHUMACKER, JR. During World War II, I had charge of one of the three vascular centers which the army had established, and off and on since then have been doing some experimental work concerned with local cold injuries We are now beginning to carry out experiments in hypothermia as related to surgical procedures Like Dr Crismon, as a consultant to the Surgeon General I had an opportunity to help plan the cold injury study program in Korea and to see it in action there.

G MALCOLM BROWN: I have been interested in cold injury since the end of the war when Queen's University first sent a party to the Arctic to study the Eskimos. In the intervening years we have been interested particularly in the vascular and metabolic aspects of the process of cold acclimatization we have sent repeated parties to the North, and also performed a series of control experiments on our own medical students at Kingston.

ALAN C. BURTON My interest in cold injury dates from the time of my conversion from physicist into physiologist by Dr J R. Murlin, of the Department of Vital Economics, University of Rochester Medical School Through his stimulation I became concerned with the heat and energy exchanges of man. Then I had the privilege of joining with the late Dr Henry C. Bazett, of the University of Pennsylvania, an enthusiast about the subject of temperature regulation, and through the war was working on problems of clothing in cold chambers, and in the field. Since the war I have tended more to study the peripheral circulation, which was the outcome of my interest in temperature regulation. However I am glad to say that at long last I am returning to my study of human calorimetry I have had very little experience in cold injury except for some work in general hypothermia.

LOUIS-PAUL DUGAL: I have been interested in cold experiments for about ten years We have been considering especially the effects and the metabolism of ascorbic acid in animals such as rats, guinea pigs, and monkeys, during exposure to cold and in attempting to discover why we obtain those effects, we have

been studying the relations between ascorbic acid and the adrenalhypophysis axis.

M. F. COFFEY For the past five years I have been involved in research in the North, and have been particularly concerned with the problems of the army in connection with severe climatic conditions. Much of this time I have been able to spend in the field, living and moving with the troops under Arctic winter conditions. So I have had my share of cold injury experience There has been time during this period for me to engage in some studies of acclimatization, the decline of manual dexterity in the cold, and hand injury under Arctic warfare conditions.

LOREN D. CARLSON: I did not do any actual work on cold injury during World War II although I experienced frostbite in the face a good many times during our high altitude work My interest in cold really began after discussions with Brigadier General O O Benson, of the U S. Air Force, concerning collaborative work between our department of the University of Washington, and the Arctic Aeromedical Laboratory at Fairbanks Alaska. Since 1948 they have very generously supported our work, which has included field trips to Fairbanks, as well as experiments in our own cold chambers My interest in the cold is really a jack-of-all-trades approach I am interested in any thing that occurs during adaptation to cold

ALBERT R. BEHNKE: I am primarily concerned with immersion hypothermia and with the physiologic reactions when the deep body temperature is lowered within a range of 30 C to 36 C. I am interested, also, in any therapeutic applications that may be made of lowered body temperatures in this range and in cold therapy particularly with reference to burns and other types of trauma.

JOSEPH R. BLAIR: Like Dr Horvath, I am indebted to the Josiah Macy Jr Foundation, and to the Defence Research Northern Laboratories for providing this Fort Churchill homecoming, for it was here in November 1946 that my interests in the effects of cold first began. For two years from 1946 to 1948, I directed a joint Canadian-British American medical test program at Fort Churchill Following that as Chief of the Cold Injury Section of the Army Medical Research Laboratory at Fort Knox, I had close association with the cold injury program in Korea, and during the past two years at Harvard Medical

School I have been associated with Drs. E. M. Landis, R. Schatzki, and J. P. Kulka in studying the late effects of cold injury.

GEORGE E. BURCH: I have not experimented extensively with cold. However, I did some work for the Office of Scientific Research and Development during the second world war concentrating on trench foot for about a year. I am interested in peripheral circulation. Recently I have been studying the "hunting reaction" of Thomas Lewis, produced by sub-zero temperatures applied locally to the hand.

EDGAR V. ALLEN: I have had a long and enduring interest in the peripheral circulation. My introduction to cold injury was the result of clinical observations and results of cold injury during World War II.

JAMES A. F. STEVENSON: My interest in cold evolved from the general problem of stress in metabolism. Active work was begun in 1950 with the support of the Defence Research Board.

EDWARD A. SELLERS: I became interested in climatic physiology in the Naval Research Division during World War II, perhaps because of a close geographical connection with Drs. Barrett, Burton, and Pagé in Toronto. At the end of the war I received support from the Defence Research Board of Canada for some general investigations which involved a study of the effects of cold. Most of my work has been in the field of acclimatization, and I am also Adviser on Medical Research and Development to the Medical Director General, Royal Canadian Navy.

M. IRENE FERRER: My own interest is in cardiovascular mechanisms, and although I have done no direct work on cold, as you all know I serve as your Editor and enjoy this task very much.

JOHN H. TALBOTT: I am interested in hypothermia, and the ill effects of cold. Before 1941 I investigated the problem of supplying protective clothing to the Quartermaster Corps, an interest which continued through 1946. I was on the Korean Frostbite project three years ago with Colonel Blair, following which the whole problem of cold injury was under consideration.

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